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(71) Applicant *(for all designated States except US)*: **MILLENNIUM PHARMACEUTICALS, INC.** [US/US]; 75 Sidney Street, Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SCHLEGEL, Robert** [US/US]; 211 Melrose Street, Auburndale, MA 02466 (US). **CHEN, Yan** [CN/US]; 26A Plymouth Street, Apartment 2, Cambridge, MA 02141 (US). **ZHAO, Xumei** [US/US]; 6 Wildwood Lane, Burlington, MA 01803 (US). **MONAHAN, John, E.** [US/US]; 942 West Street, Walpole, MA 02081 (US). **KAMATKAR, Shubhangi** [IN/US]; 655 Saw Mill Brook Parkway, #1, Newton, MA 02459 (US). **GANNAVARAPU, Manjula** [IN/US]; 10 Windemere Drive, Acton, MA 01720 (US). **GLATT, Karen** [US/US]; 17 Beacon Street, Natick, MA 01760 (US). **HOERSCH, Sebastian** [DE/US]; 127 Brattle Street, Arlington, MA 02424 (US).

(74) Agents: **SMITH, DeAnn, F.** et al.; Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109 (US).

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(54) **Title:** NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF CERVICAL CANCER

(57) **Abstract:** The invention relates to newly discovered nucleic acid molecules and proteins associated with cervical cancer including pre-malignant conditions such as dysplasia. Compositions, kits, and methods for detecting, characterizing, preventing, and treating human cervical cancers are provided.

NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF CERVICAL CANCER

RELATED APPLICATIONS

The present application claims priority to U.S. provisional patent application serial no. 60/298,159, filed on June 13, 2001, U.S. provisional patent application serial no. 60/298,155, filed on June 13, 2001, and U.S. provisional patent application serial no. 60/335,936, filed on November 14, 2001, all of which are expressly incorporated by reference.

FIELD OF THE INVENTION

The field of the invention is cervical cancer, including diagnosis, characterization, management, and therapy of cervical cancer.

BACKGROUND OF THE INVENTION

The increased number of cancer cases reported in the United States, and, indeed, around the world, is a major concern. Currently there are only a handful of treatments available for specific types of cancer, and these provide no absolute guarantee of success. In order to be most effective, these treatments require not only an early detection of the malignancy, but a reliable assessment of the severity of the malignancy.

Cancer of the cervix is one of the most common malignancies in women and remains a significant public health problem throughout the world. In the United States alone, invasive cervical cancer accounts for approximately 19% of all gynecological cancers. In 1996, it was estimated that there were 14,700 newly diagnosed cases and 4900 deaths attributed to this disease (American Cancer Society, Cancer Facts & Figures 1996, Atlanta, Ga.: American Cancer Society, 1996). In many developing countries, where mass screening programs are not widely available, the clinical problem is more serious. Worldwide, the number of new cases is estimated to be 471,000 with a four-year survival rate of only 40% (Munoz et al., 1989, *Epidemiology of Cervical Cancer* In: "Human Papillomavirus", New York, Oxford Press, pp 9-39; National Institutes of Health, Consensus Development Conference Statement on Cervical Cancer, Apr.1-3, 1996).

The precursor to cervical cancer is dysplasia, also known in the art as cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL). While it is not understood how normal cells become transformed, the concept of a continuous spectrum of histopathological change from normal, stratified epithelium through CIN to invasive cancer has been widely accepted for many years. A large body of epidemiological and molecular biological evidence has established human papillomavirus (HPV) infection as a causative factor in cervical cancer. HPV is found in 85% or more of squamous cell invasive lesions, which represent the most common histologic type seen in cervical carcinoma. Additional cofactors have also been identified, including oncogenes that have been activated by point mutations and chromosomal translocations or deletions.

In light of this, cervical cancer remains a highly preventable form of cancer when pre-invasive lesions are detected early. Cytological examination of Papanicolaou-stained cervical smears (also referred to as Pap smears) is currently the principle method for detecting cervical cancer. Not surprisingly, the effectiveness of Pap smear screening varies depending not only upon the quality of the sample being used, but also upon subjective parameters that are inherent to the analysis. In addition, despite the historical success of the test, concerns have arisen regarding its ability to reliably predict the behavior of some pre-invasive lesions (Ostor *et al.*, 1993, *Int. J. Gynecol. Pathol.* 12: 186-192; and Genest *et al.*, 1993, *Human Pathol.* 24: 730-736).

SUMMARY OF THE INVENTION

The invention relates to cancer markers (hereinafter "markers" or "markers of the inventions"), which are listed in Table 1. The invention provides nucleic acids and proteins that are encoded by or correspond to the markers (hereinafter "marker nucleic acids" and "marker proteins," respectively). Table 1 provides the sequence identifiers of the sequences of such marker nucleic acids and proteins listed in the accompanying Sequence Listing. The invention further provides antibodies, antibody derivatives and antibody fragments which bind specifically with such proteins and/or fragments of the proteins.

The invention also relates to various methods, reagents and kits for diagnosing, staging, prognosing, monitoring and treating cervical cancer. "Cervical cancer " as used herein includes carcinomas, (*e.g.*, carcinoma in situ, invasive

carcinoma, metastatic carcinoma) and pre-malignant conditions, (*e.g.*, dysplasia, including CIN or SIL). In one embodiment, the invention provides a diagnostic method of assessing whether a patient has cervical cancer or has higher than normal risk for developing cervical cancer, comprising the steps of comparing the level of expression of a marker of the invention in a patient sample and the normal level of expression of the marker in a control, *e.g.*, a sample from a patient without cervical cancer. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer or has higher than normal risk for developing cervical cancer.

According to the invention, the markers are selected such that the positive predictive value of the methods of the invention is at least about 10%, preferably about 25%, more preferably about 50% and most preferably about 90%. Also preferred for use in the methods of the invention are markers that are differentially expressed, as compared to normal cervical cells, by at least two-fold in at least about 20%,more preferably about 50% and most preferably about 75% of any of the following conditions: stage 0 cervical cancer patients, stage I cervical cancer patients, stage II cervical cancer patients, stage III cervical cancer patients, stage IV cervical cancer patients, grade I cervical cancer patients, grade II cervical cancer patients, grade III cervical cancer patients, squamous cell (epidermoid) cervical cancer patients, cervical adenocarcinoma patients, cervical adenosquamous carcinoma patients, small-cell cervical carcinoma patients, malignant cervical cancer patients, patients with primary carcinomas of the cervix, patients with primary malignant lymphomas of the cervix and patients with secondary malignant lymphomas of the cervix, and all other types of cancers, malignancies and transformations associated with the cervix.

In a preferred diagnostic method of assessing whether a patient is afflicted with cervical cancer (*e.g.*, new detection ("screening"), detection of recurrence, reflex testing), the method comprises comparing:

a) the level of expression of a marker of the invention in a patient sample, and

b) the normal level of expression of the marker in a control non-cervical cancer sample.

A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer.

The invention also provides diagnostic methods for assessing the efficacy of a therapy for inhibiting cervical cancer in a patient. Such methods comprise comparing:

a) expression of a marker of the invention in a first sample obtained from the patient prior to providing at least a portion of the therapy to the patient, and

b) expression of the marker in a second sample obtained from the patient following provision of the portion of the therapy.

A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the therapy is efficacious for inhibiting cervical cancer in the patient.

It will be appreciated that in these methods the "therapy" may be any therapy for treating cervical cancer including, but not limited to, chemotherapy, radiation therapy, surgical removal of tumor tissue, gene therapy and biologic therapy such as the administering of antibodies and chemokines. Thus, the methods of the invention may be used to evaluate a patient before, during and after therapy, for example, to evaluate the reduction in tumor burden.

In a preferred embodiment, the diagnostic methods are directed to therapy using a chemical or biologic agent. These methods comprise comparing:

a) expression of a marker of the invention in a first sample obtained from the patient and maintained in the presence of the chemical or biologic agent, and

b) expression of the marker in a second sample obtained from the patient and maintained in the absence of the agent.

A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the agent is efficacious for inhibiting cervical cancer, in the patient. In one embodiment, the first and second samples can be portions of a single sample obtained from the patient or portions of pooled samples obtained from the patient.

The invention additionally provides a monitoring method for assessing the progression of cervical cancer in a patient, the method comprising:

a) detecting in a patient sample at a first time point, the expression of a marker of the invention;

b) repeating step a) at a subsequent time point in time; and

c) comparing the level of expression detected in steps a) and b), and therefrom monitoring the progression of cervical cancer in the patient.

A significantly higher level of expression of the marker in the sample at the subsequent time point from that of the sample at the first time point is an indication that the cervical cancer has progressed, whereas a significantly lower level of expression is an indication that the cervical cancer has regressed.

The invention further provides a diagnostic method for determining whether cervical cancer has metastasized or is likely to metastasize in the future, the method comprising comparing:

a) the level of expression of a marker of the invention in a patient sample, and

b) the normal level (or non-metastatic level) of expression of the marker in a control sample.

A significantly higher level of expression in the patient sample as compared to the normal level (or non-metastatic level) is an indication that the cervical cancer has metastasized or is likely to metastasize in the future.

The invention moreover provides a test method for selecting a composition for inhibiting cervical cancer in a patient. This method comprises the steps of:

a) obtaining a sample comprising cancer cells from the patient;

b) separately maintaining aliquots of the sample in the presence of a plurality of test compositions;

c) comparing expression of a marker of the invention in each of the aliquots; and

d) selecting one of the test compositions which significantly reduces the level of expression of the marker in the aliquot containing that test composition, relative to the levels of expression of the marker in the presence of the other test compositions.

The invention additionally provides a test method of assessing the cervical carcinogenic potential of a compound. This method comprises the steps of:

a) maintaining separate aliquots of cervical cells in the presence and absence of the compound; and

b) comparing expression of a marker of the invention in each of the aliquots.

A significantly higher level of expression of the marker in the aliquot maintained in the presence of the compound, relative to that of the aliquot maintained in the absence of the compound, is an indication that the compound possesses cervical carcinogenic potential.

In addition, the invention further provides a method of inhibiting cervical cancer in a patient. This method comprises the steps of:

a) obtaining a sample comprising cancer cells from the patient;

b) separately maintaining aliquots of the sample in the presence of a plurality of compositions;

c) comparing expression of a marker of the invention in each of the aliquots; and

d) administering to the patient at least one of the compositions which significantly lowers the level of expression of the marker in the aliquot containing that composition, relative to the levels of expression of the marker in the presence of the other compositions.

In the aforementioned methods, the samples or patient samples comprise cells obtained from the patient. The cells may be found in a cervical smear collected, for example, by a cervical brush. In another embodiment, the sample is a body fluid. Such fluids include, for example, blood fluids, lymph, ascitic fluids, gynecological fluids, urine, and fluids collected by vaginal rinsing. In a further embodiment, the patient sample is *in vivo*.

According to the invention, the level of expression of a marker of the invention in a sample can be assessed, for example, by detecting the presence in the sample of:

- the corresponding marker protein (*e.g.*, a protein having one of the sequences set forth as "SEQ ID NO (AAs)" in Table 1, or a fragment of the protein (*e.g.* by using a reagent, such as an antibody, an antibody derivative,

an antibody fragment or single-chain antibody, which binds specifically with the protein or protein fragment)

- the corresponding marker nucleic acid (*e.g.* a nucleotide transcript having one of the nucleic acid sequences set forth as "SEQ ID NO (nts)" in Table 1, or a complement thereof), or a fragment of the nucleic acid (*e.g.* by contacting transcribed polynucleotides obtained from the sample with a substrate having affixed thereto one or more nucleic acids having the entire or a segment of the nucleic acid sequence of any of the SEQ ID NO (nts), or a complement thereof)
- a metabolite which is produced directly (*i.e.*, catalyzed) or indirectly by the corresponding marker protein.

According to the invention, any of the aforementioned methods may be performed using a plurality (*e.g.* 2, 3, 5, or 10 or more) of cervical cancer markers, including cervical cancer markers known in the art. In such methods, the level of expression in the sample of each of a plurality of markers, at least one of which is a marker of the invention, is compared with the normal level of expression of each of the plurality of markers in samples of the same type obtained from control humans not afflicted with cervical cancer. A significantly altered (*i.e.*, increased or decreased as specified in the above-described methods using a single marker) level of expression in the sample of one or more markers of the invention, or some combination thereof, relative to that marker's corresponding normal or control level, is an indication that the patient is afflicted with cervical cancer. For all of the aforementioned methods, the marker(s) are preferably selected such that the positive predictive value of the method is at least about 10%.

In a further aspect, the invention provides an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein (*e.g.*, a protein having one of the amino acid sequences set forth in the Sequence Listing) or a fragment of the protein. The invention also provides methods for making such antibody, antibody derivative, and antibody fragment. Such methods may comprise immunizing a mammal with a protein or peptide comprising the entirety, or a segment of 10 or more amino acids, of a marker protein (*e.g.*, a protein having one of the amino acid sequences set forth in the Sequence Listing), wherein the protein or peptide may be obtained from a cell or by chemical synthesis. The methods of the invention also encompass producing

monoclonal and single-chain antibodies, which would further comprise isolating splenocytes from the immunized mammal, fusing the isolated splenocytes with an immortalized cell line to form hybridomas, and screening individual hybridomas for those that produce an antibody that binds specifically with a marker protein or a fragment of the protein.

In another aspect, the invention relates to various diagnostic and test kits. In one embodiment, the invention provides a kit for assessing whether a patient is afflicted with cervical cancer. The kit comprises a reagent for assessing expression of a marker of the invention. In another embodiment, the invention provides a kit for assessing the suitability of a chemical or biologic agent for inhibiting cervical cancer in a patient. Such a kit comprises a reagent for assessing expression of a marker of the invention, and may also comprise one or more of such agents. In a further embodiment, the invention provides kits for assessing the presence of cervical cancer cells or treating cervical cancers. Such kits comprise an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein, or a fragment of the protein. Such kits may also comprise a plurality of antibodies, antibody derivatives, or antibody fragments wherein the plurality of such antibody agents binds specifically with a marker protein, or a fragment of the protein.

In an additional embodiment, the invention also provides a kit for assessing the presence of cervical cancer cells, wherein the kit comprises a nucleic acid probe that binds specifically with a marker nucleic acid or a fragment of the nucleic acid. The kit may also comprise a plurality of probes, wherein each of the probes binds specifically with a marker nucleic acid, or a fragment of the nucleic acid.

In a further aspect, the invention relates to methods for treating a patient afflicted with cervical cancer or at risk of developing cervical cancer. Such methods may comprise reducing the expression and/or interfering with the biological function of a marker of the invention. In one embodiment, the method comprises providing to the patient an antisense oligonucleotide or polynucleotide complementary to a marker nucleic acid, or a segment thereof. For example, an antisense polynucleotide may be provided to the patient through the delivery of a vector that expresses an anti-sense polynucleotide of a marker nucleic acid or a fragment thereof. In another embodiment, the method comprises providing to the patient an antibody, an antibody derivative, or antibody fragment, which binds specifically with a marker protein or a fragment of the

protein. In a preferred embodiment, the antibody, antibody derivative or antibody fragment binds specifically with a protein having one of the amino acid sequences set forth in the Sequence Listing, or a fragment of the protein.

It will be appreciated that the methods and kits of the present invention may also include known cancer markers including known cervical cancer markers. It will further be appreciated that the methods and kits may be used to identify cancers other than cervical cancer.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to newly discovered cancer markers associated with the cancerous state of cervical cells. It has been discovered that the higher than normal level of expression of any of these markers or combination of these markers correlates with the presence of cervical cancer including pre-malignant conditions such as dysplasia, in a patient. Methods are provided for detecting the presence of cervical cancer in a sample, the absence of cervical cancer in a sample, the stage of a cervical cancer, and other characteristics of cervical cancer that are relevant to prevention, diagnosis, characterization, and therapy of cervical cancer in a patient. Methods of treating cervical cancer are also provided.

Table 1 lists the markers of the invention which are over-expressed in cervical cancer cells compared to normal (*i.e.,* non-cancerous) cervical cells and comprises markers listed in Tables 2 and 3.. Table 2 lists newly-identified nucleotide and amino acid sequences. Table 3 lists newly-identified nucleotide sequences. Tables 1-3 provide the sequence listing identifiers of the cDNA sequence of a nucleotide transcript and the amino acid sequence of a protein encoded by or corresponding to each marker, as well as the location of the protein coding sequence within the cDNA sequence.

Table 1

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M661	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 1	1	2	223..11946
M662	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 2	3	4	223..11922
M663	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 3	5	6	223..12000
M664	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 4	7	8	223..11976
M1	APOL1: Apolipoprotein L-I mNA, splice variant A, major form	9	10	213..1364
M2	APOL1: Apolipoprotein L-I mNA, splice variant B, minor form	11	12	274..1518
M3	APOL3: apolipoprotein L, 3; TNF-inducible protein CG12-1	13	14	418..1413
OV3	AQP5: Aquaporin 5	15	16	519..1316
M4	BC001980: clone MGC:5618	17	18	157..225
M5	BST2: Bone marrow stromal cell antigen 2	19	20	10..552
M6	BTEB1: basic transcription element binding protein 1	21	22	1265..1999
M665	CD74: CD74 antigen (invariant polypeptide of major histocompatibility complex,class II antigen-associated)	23	24	8..706
M7	CDC20: CDC20 cell cycle protein	25	26	45..1544
M8	CDKN2C: cyclin-dependent kinase inhibitor 2C, p18	27	28	1216..1722
M9	CKTSF1B1: (cysteine knot superfamily 1, BMP antagonist 1), gremlin	29	30	45..1544
M10	CLDN1: claudin 1	31	32	221..856
M11	CLIC4: chloride intracellular channel 4	33	34	198..959
M12	COL1A1: collagen, type I, alpha 1	35	36	120..4514
M13	COL1A2: collagen, type I, alpha 2	37	38	140..4240
M14	COL8A1: collagen, type VIII, alpha 1	39	40	1..2235
M15	COPA: coatomer protein complex, subunit alpha	41	42	467..4141
M16	CRIP1: cysteine-rich protein 1 (intestinal)	43	44	1..234
M17	CTGF: connective tissue growth factor	45	46	146..1195
M18	DOC: downregulated in ovarian cancer 1	47	48	135..2393
M19	EFNA1: ephrin-A1	49	50	74..691
M481	EPPK1: epiplakin 1	51	52	89..15286
M20	FLJ11350: hypothetical protein FLJ11350	53	54	106..1047
M21	FLJ13809: hypothetical protein FLJ13809	55	56	64..1593
M22	FLJ20500: hypothetical protein FLJ20500	57	58	198..896
M23	FLJ23399: hypothetical protein FLJ23399	59	60	283..1770
M24	FN1: Fibronectin 1, variant 1	61	62	<1..2384
M25	FN1: Fibronectin 1, variant 2	63	64	<1..6988
M482	FOSL2: FOS-like antigen 2, variant 1	65	66	324..1304
M483	FOSL2: FOS-like antigen 2, variant 2	67	66	324..1304
M484	FSHPRH1: FSH primary response (LRPR1, rat) homolog 1	68	69	270..2540
M26	FY: Duffy blood group	70	71	495..1511

M485	G1P3:interferon, alpha-inducible protein (clone IFI-6-16)	72	73	108..500
M486	GW112: GW112 protein	74	75	509..1072
M27	HSKERUV: clone 266, Human radiated keratinocyte mRNA 266 (keratin-related protein)	76	77	<1..801
M28	HSPC121: butyrate-induced transcript 1	78	79	150..1271
M29	HUMCLPB: Coactosin like protein	80	81	150..576
M487	hypothetical protein	82	83	58..8163
M30	IFI27: (interferon, alpha-inducible protein 27	84	85	55..423
OV31	IFI30: interferon, gamma-inducible protein 30	86	87	41..952
M31	IFITM2: interferon induced transmembrane protein 2 (1-8D)	88	89	280..678
M32	IGFBP-3: insulin-like growth factor binding protein 3	90	91	133..1009
M33	IL8RA: interleukin 8	92	93	75..374
M34	INHBA: Inhibin, beta-1	94	95	86..1366
M488	ITGA3: integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor), variant a	96	97	74..3229
M454	ITGA3: integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor), variant b	98	99	74..3274
M35	ITGB6: integrin, beta 6	100	101	195..2561
M36	KATII: L-kynurenine/alpha-aminoadipate aminotransferase	102	103	454..1731
M666	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 1	104	105	89..1315
M667	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 2	106	107	54..1313
M668	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 3	108	109	28..1233
M37	KIAA0662: KIAA0662 protein	110	111	<1..2035
M38	LAMA3: Laminin, alpha-3 (nicein (150kD), (kalinin (165kD), BM600 (150kD)	112	113	1..5142
M39	LAMC2: laminin, gamma 2	114	115	90..3671
M40	LSM5: U6 snRNA-associated Sm-like protein	116	117	1..276
M41	LUM: lumican	118	119	85..1101
M42	MACMARCKS: macrophage myristoylated alanine-rich C kinase substrate	120	121	14..601
M43	MAGP: microfibrillar-associated protein 2 precursor, transcript variant 1	122	123	115..666
M44	MAGP: microfibrillar-associated protein 2 precursor, transcript variant 2	124	125	100..651
M45	MAPK: mitogen-activated protein kinase 1	126	127	328..1410
M489	MCM6: minichromosome maintenance deficient (mis5, S. pombe) 6	128	129	62..2527
M46	MDK: midkine (neurite growth-promoting factor 2)	130	131	26..457
M47	MGP: matrix Gla protein	132	133	47..358
M48	MMP12: matrix metalloproteinase 12	134	135	13..1425
M49	MMP3: matrix metalloproteinase 3, stromelysin 1, progelatinase	136	137	64..1497
M294	MMP7: matrix metalloproteinase 7 (matrilysin, uterine), PUMP1 proteinase, variant 1	138	139	48..851
OV52	MMP7: matrix metalloproteinase 7 (matrilysin, uterine), PUMP1 proteinase, variant 2	140	139	28..831

M50	MMP9: matrix metalloproteinase 9, gelatinase B, 92kD gelatinase, 92kD type IV collagenase	141	142	20..2143
OV68	MSLN: mesothelin, variant 1	143	144	88..2196
OV69	MSLN: mesothelin, variant 2	145	146	88..1980
OV70	MSLN: mesothelin, variant 3	147	148	88..1950
OV71	MSLN: mesothelin, variant 4	149	150	88..2172
OV72	MSLN: mesothelin, variant 5	151	152	88..1926
OV43	MSLN: mesothelin, variant 6	153	154	88..1956
OV45	MUC1: mucin 1, transmembrane, variant 1	155	156	58..1605
M669	MUC1: mucin 1, transmembrane, variant 2	157	158	74..3841
M51	MYBL2: v-myb avian myeloblastosis viral oncogene homolog-like 2	159	160	128..2230
M52	MYH11: smooth muscle myosin heavy chain 11, isoform SM1	161	162	89..6007
M53	MYH11: smooth muscle myosin heavy chain 11, isoform SM2	163	164	89..5905
M54	NK4: natural killer cell transcript 4 , variant 1	165	166	60..764
M670	NK4: natural killer cell transcript 4 , variant 2	167	168	60..764
M55	NP25: (neuronal protein)	169	170	50..898
OV48	OPN-a (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	171	172	1..942
OV49	OPN-b (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	173	174	88..990
OV50	OPN-c (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	175	176	1..861
M56	OSF-2, osteoblast specific factor 2 (fasciclin I-like), variant 1	177	178	12..2522
M491	OSF-2, osteoblast specific factor 2 (fasciclin I-like), variant 2	179	180	28..2367
M57	PIM2: pim-2 oncogene	181	182	186..1190
M58	PLAU: plasminogen activator, urokinase	183	184	77..1372
M59	PLK: polo (Drosophia)-like kinase	185	186	64..1875
M671	PNN: pinin, desmosome associated protein	187	188	31..2262
M60	PRG1: proteoglycan 1, secretory granule	189	190	25..501
M61	PTHLH: parathyroid hormone-like hormone	191	192	304..831
M62	PTN: pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)	193	194	1542..2048
M63	RAB6KIFL: RAB6 interacting, kinesin-like (rabkinesin6)	195	196	28..2700
M64	RARRES3: retinoic acid receptor responder (tazarotene induced) 3	197	198	62..556
M65	RBP1: retinol-binding protein 1(cellular), CRABP-I, CRBP-I	199	200	126..533
M66	RGS16: Regulator of G protein signaling-16	201	202	93..701
M67	S100A2: S100 calcium binding protein A2, variant 1	203	204	72..362
M68	S100A2: S100 calcium binding protein A2, variant 2	205	206	41..334
M69	SCYA20: small inducible cytokine subfamily A (Cys-Cys), member 20	207	208	59..349
M70	SPARC: Osteonectin (secreted protein, acidic, cysteine-rich)	209	210	58..969
M71	STCH: stress 70 protein chaperone, microsome-associated	211	212	37..1452
M492	STK12: serine/ threonine kinase 12	213	214	58..1092

M72	TK1: thymidine kinase 1, soluble	215	216	58..762
OV86	TMPRSS4: transmembrane protease, serine 4	217	218	310..1623
M73	TMSB4X: thymosin, beta 4, X chromosome	219	220	78..212
M74	TOP2A: topoisomerase (DNA) II alpha (170kD)	221	222	37..4632
M493	TPM1: tropomyosin 1 (alpha)	223	224	57..911
M75	TXN: thioredoxin	225	226	64..381
M76	UBCH10: ubiquitin carrier protein E2-C	227	228	41..580
M77	UBD: diubiquitin	229	230	19..516
M78	unnamed gene (1)	231	232	45..1353
M79	unnamed gene (2)	233	234	1..1508
M80	VATD: vacuolar proton pump delta polypeptide	235	236	166..909
M81	ZWINT: ZW10 interactor	237	238	25..858

Table 2

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M661	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 1	1	2	223..11946
M662	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 2	3	4	223..11922
M663	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 3	5	6	223..12000
M664	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 4	7	8	223..11976
OV68	MSLN: mesothelin, variant 1	143	144	88..2196
OV69	MSLN: mesothelin, variant 2	145	146	88..1980
OV70	MSLN: mesothelin, variant 3	147	148	88..1950
OV71	MSLN: mesothelin, variant 4	149	150	88..2172
OV72	MSLN: mesothelin, variant 5	151	152	88..1926
M670	NK4: natural killer cell transcript 4 , variant 2	167	168	60..764
M67	S100A2: S100 calcium binding protein A2, variant 1	203	204	72..362
OV86	TMPRSS4: transmembrane protease, serine 4	217	218	310..1623
M78	unnamed gene (1)	231	232	45..1353
M79	unnamed gene (2)	233	234	1..1508

Table 3

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M481	EPPK1: epiplakin 1	51	52	89..15286
M482	FOSL2: FOS-like antigen 2, variant 1	65	66	324..1304
M483	FOSL2: FOS-like antigen 2, variant 2	67	66	324..1304
M484	FSHPRH1: FSH primary response (LRPR1, rat) homolog 1	68	69	270..2540
M35	ITGB6: integrin, beta 6	100	101	195..2561
OV43	MSLN: mesothelin, variant 6	153	154	88..1956

Definitions

As used herein, each of the following terms has the meaning associated with it in this section.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.* to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

A "marker" is a gene whose altered level of expression in a tissue or cell from its expression level in normal or healthy tissue or cell is associated with a disease state, such as cancer. A "marker nucleic acid" is a nucleic acid (*e.g.*, mRNA, cDNA) encoded by or corresponding to a marker of the invention. Such marker nucleic acids include DNA (*e.g.*, cDNA) comprising the entire or a partial sequence of any of the nucleic acid sequences set forth in the Sequence Listing or the complement of such a sequence. The marker nucleic acids also include RNA comprising the entire or a partial sequence of any of the nucleic acid sequences set forth in the Sequence Listing or the complement of such a sequence, wherein all thymidine residues are replaced with uridine residues. A "marker protein" is a protein encoded by or corresponding to a marker of the invention. A marker protein comprises the entire or a partial sequence of any of the sequences set forth in the Sequence Listing. The terms "protein" and "polypeptide' are used interchangeably.

The term "probe" refers to any molecule which is capable of selectively binding to a specifically intended target molecule, for example, a nucleotide transcript or protein encoded by or corresponding to a marker. Probes can be either synthesized by one skilled in the art, or derived from appropriate biological preparations. For purposes of detection of the target molecule, probes may be specifically designed to be labeled, as

described herein. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

A "cervical-associated" body fluid is a fluid which, when in the body of a patient, contacts or passes through cervical cells or into which cells or proteins shed from cervical cells are capable of passing. The cells may be found in a cervical smear collected, for example, by a cervical brush. Exemplary cervical-associated body fluids include blood fluids, lymph, ascitic fluids, gynecological fluids, cystic fluid, urine, and fluids collected by vaginal rinsing.

The "normal" level of expression of a marker is the level of expression of the marker in cervical cells of a human subject or patient not afflicted with cervical cancer

An "over-expression" or "significantly higher level of expression" of a marker refers to an expression level in a test sample that is greater than the standard error of the assay employed to assess expression, and is preferably at least twice, and more preferably three, four, five or ten times the expression level of the marker in a control sample (*e.g.*, sample from a healthy subjects not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

A "significantly lower level of expression" of a marker refers to an expression level in a test sample that is at least twice, and more preferably three, four, five or ten times lower than the expression level of the marker in a control sample (*e.g.*, sample from a healthy subject not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

As used herein, the term "promoter/regulatory sequence" means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue-specific manner.

A "constitutive" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell under most or all physiological conditions of the cell.

An "inducible" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only when an inducer which corresponds to the promoter is present in the cell.

A "tissue-specific" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

A "transcribed polynucleotide" or "nucleotide transcript" is a polynucleotide (*e.g.* an mRNA, hnRNA, a cDNA, or an analog of such RNA or cDNA) which is complementary to or homologous with all or a portion of a mature mRNA made by transcription of a marker of the invention and normal post-transcriptional processing (*e.g.* splicing), if any, of the RNA transcript, and reverse transcription of the RNA transcript.

"Complementary" refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds ("base pairing") with a residue of a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region is capable of base pairing with a residue of the second region. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residues of the first portion are capable of base pairing

with nucleotide residues in the second portion. More preferably, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

"Homologous" as used herein, refers to nucleotide sequence similarity between two regions of the same nucleic acid strand or between regions of two different nucleic acid strands. When a nucleotide residue position in both regions is occupied by the same nucleotide residue, then the regions are homologous at that position. A first region is homologous to a second region if at least one nucleotide residue position of each region is occupied by the same residue. Homology between two regions is expressed in terms of the proportion of nucleotide residue positions of the two regions that are occupied by the same nucleotide residue. By way of example, a region having the nucleotide sequence 5'-ATTGCC-3' and a region having the nucleotide sequence 5'-TATGGC-3' share 50% homology. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residue positions of each of the portions are occupied by the same nucleotide residue. More preferably, all nucleotide residue positions of each of the portions are occupied by the same nucleotide residue.

A molecule is "fixed" or “affixed” to a substrate if it is covalently or non-covalently associated with the substrate such the substrate can be rinsed with a fluid (*e.g.* standard saline citrate, pH 7.4) without a substantial fraction of the molecule dissociating from the substrate.

As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in an organism found in nature.

A cancer is "inhibited" if at least one symptom of the cancer is alleviated, terminated, slowed, or prevented. As used herein, cervical cancer is also "inhibited" if recurrence or metastasis of the cancer is reduced, slowed, delayed, or prevented.

A kit is any manufacture (*e.g.* a package or container) comprising at least one reagent, *e.g.* a probe, for specifically detecting the expression of a marker of the invention. The kit may be promoted, distributed, or sold as a unit for performing the methods of the present invention.

"Proteins of the invention" encompass marker proteins and their fragments; variant marker proteins and their fragments; peptides and polypeptides comprising an at least 15 amino acid segment of a marker or variant marker protein; and fusion proteins comprising a marker or variant marker protein, or an at least 15 amino acid segment of a marker or variant marker protein.

Unless otherwise specified herewithin, the terms "antibody" and "antibodies" broadly encompass naturally-occurring forms of antibodies (*e.g.*, IgG, IgA, IgM, IgE) and recombinant antibodies such as single-chain antibodies, chimeric and humanized antibodies and multi-specific antibodies, as well as fragments and derivatives of all of the foregoing, which fragments and derivatives have at least an antigenic binding site. Antibody derivatives may comprise a protein or chemical moiety conjugated to an antibody.

<u>Description</u>

The present invention is based, in part, on newly identified markers which are over-expressed in cervical cancer cells as compared to their expression in normal (*i.e.* non-cancerous) cervical cells. The enhanced expression of one or more of these markers in cervical cells is herein correlated with the cancerous state of the tissue. The invention provides compositions, kits, and methods for assessing the cancerous state of cervical cells (*e.g.* cells obtained from a human, cultured human cells, archived or preserved human cells and *in vivo* cells) as well as treating patients afflicted with cervical cancer.

The compositions, kits, and methods of the invention have the following uses, among others:

1) assessing whether a patient is afflicted with cervical cancer;
2) assessing the stage of cervical cancer in a human patient;
3) assessing the grade of cervical cancer in a patient;
4) assessing the benign or malignant nature of cervical cancer in a patient;
5) assessing the metastatic potential of cervical cancer in a patient;
6) assessing the histological type of neoplasm associated with cervical cancer in a patient;

7) making antibodies, antibody fragments or antibody derivatives that are useful for treating cervical cancer and/or assessing whether a patient is afflicted with cervical cancer;

8) assessing the presence of cervical cancer cells;

9) assessing the efficacy of one or more test compounds for inhibiting cervical cancer in a patient;

10) assessing the efficacy of a therapy for inhibiting cervical cancer in a patient;

11) monitoring the progression of cervical cancer in a patient;

12) selecting a composition or therapy for inhibiting cervical cancer in a patient;

13) treating a patient afflicted with cervical cancer;

14) inhibiting cervical cancer in a patient;

15) assessing the cervical carcinogenic potential of a test compound; and

16) preventing the onset of cervical cancer in a patient at risk for developing cervical cancer.

The invention thus includes a method of assessing whether a patient is afflicted with cervical cancer which includes assessing whether the patient has pre-metastasized cervical cancer. This method comprises comparing the level of expression of a marker of the invention (listed in Table 1) in a patient sample and the normal level of expression of the marker in a control, *e.g.,* a non-cervical cancer sample. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer.

Gene delivery vehicles, host cells and compositions (all described herein) containing nucleic acids comprising the entirety, or a segment of 15 or more nucleotides, of any of the nucleic acid sequences set forth in the Sequence Listing, or the complement of such sequences, and polypeptides comprising the entirety, or a segment of 10 or more amino acids, of any of the amino acid sequences set forth in the Sequence Listing, are also provided by this invention.

As described herein, cervical cancer in patients is associated with an increased level of expression of one or more markers of the invention. While, as discussed above, some of these changes in expression level result from occurrence of the

cervical cancer, others of these changes induce, maintain, and promote the cancerous state of cervical cancer cells. Thus, cervical cancer characterized by an increase in the level of expression of one or more markers of the invention can be inhibited by reducing and/or interfering with the expression of the markers and/or function of the proteins encoded by those markers.

Expression of a marker of the invention can be inhibited in a number of ways generally known in the art. For example, an antisense oligonucleotide can be provided to the cervical cancer cells in order to inhibit transcription, translation, or both, of the marker(s). Alternately, a polynucleotide encoding an antibody, an antibody derivative, or an antibody fragment which specifically binds a marker protein, and operably linked with an appropriate promoter/regulator region, can be provided to the cell in order to generate intracellular antibodies which will inhibit the function or activity of the protein. The expression and/or function of a marker may also be inhibited by treating the cervical cancer cell with an antibody, antibody derivative or antibody fragment that specifically binds a marker protein. Using the methods described herein, a variety of molecules, particularly including molecules sufficiently small that they are able to cross the cell membrane, can be screened in order to identify molecules which inhibit expression of a marker or inhibit the function of a marker protein. The compound so identified can be provided to the patient in order to inhibit cervical cancer cells of the patient.

Any marker or combination of markers of the invention, as well as any known markers in combination with the markers of the invention, may be used in the compositions, kits, and methods of the present invention. In general, it is preferable to use markers for which the difference between the level of expression of the marker in cervical cancer cells and the level of expression of the same marker in normal cervical cells is as great as possible. Although this difference can be as small as the limit of detection of the method for assessing expression of the marker, it is preferred that the difference be at least greater than the standard error of the assessment method, and preferably a difference of at least 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 100-, 500-, 1000-fold or greater than the level of expression of the same marker in normal cervical tissue.

It is recognized that certain marker proteins are secreted from cervical cells (*i.e.* one or both of normal and cancerous cells) to the extracellular space surrounding the cells. These markers are preferably used in certain embodiments of the compositions, kits, and methods of the invention, owing to the fact that the such marker proteins can be detected in a cervical-associated body fluid sample, which may be more easily collected from a human patient than a tissue biopsy sample. In addition, preferred *in vivo* techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

It is a simple matter for the skilled artisan to determine whether any particular marker protein is a secreted protein. In order to make this determination, the marker protein is expressed in, for example, a mammalian cell, preferably a human cervical cell line, extracellular fluid is collected, and the presence or absence of the protein in the extracellular fluid is assessed (*e.g.* using a labeled antibody which binds specifically with the protein).

The following is an example of a method which can be used to detect secretion of a protein. About 8×10^5 293T cells are incubated at 37°C in wells containing growth medium (Dulbecco's modified Eagle's medium {DMEM} supplemented with 10% fetal bovine serum) under a 5% (v/v) CO_2, 95% air atmosphere to about 60-70% confluence. The cells are then transfected using a standard transfection mixture comprising 2 micrograms of DNA comprising an expression vector encoding the protein and 10 microliters of LipofectAMINE™ (GIBCO/BRL Catalog no. 18342-012) per well. The transfection mixture is maintained for about 5 hours, and then replaced with fresh growth medium and maintained in an air atmosphere. Each well is gently rinsed twice with DMEM which does not contain methionine or cysteine (DMEM-MC; ICN Catalog no. 16-424- 54). About 1 milliliter of DMEM-MC and about 50 microcuries of Trans-^{35}S™ reagent (ICN Catalog no. 51006) are added to each well. The wells are maintained under the 5% CO_2 atmosphere described above and incubated at 37°C for a selected period. Following incubation, 150 microliters of conditioned medium is removed and centrifuged to remove floating cells and debris.

The presence of the protein in the supernatant is an indication that the protein is secreted.

It will be appreciated that patient samples containing cervical cells may be used in the methods of the present invention. In these embodiments, the level of expression of the marker can be assessed by assessing the amount (*e.g.* absolute amount or concentration) of the marker in a cervical cell sample, *e.g.*, cervical smear obtained from a patient. The cell sample can, of course, be subjected to a variety of well-known post-collection preparative and storage techniques (*e.g.*, nucleic acid and/or protein extraction, fixation, storage, freezing, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to assessing the amount of the marker in the sample. Likewise, cervical smears may also be subjected to post-collection preparative and storage techniques, *e.g.*, fixation.

The compositions, kits, and methods of the invention can be used to detect expression of marker proteins having at least one portion which is displayed on the surface of cells which express it. It is a simple matter for the skilled artisan to determine whether a marker protein, or a portion thereof, is exposed on the cell surface. For example, immunological methods may be used to detect such proteins on whole cells, or well known computer-based sequence analysis methods may be used to predict the presence of at least one extracellular domain (*i.e.* including both secreted proteins and proteins having at least one cell-surface domain). Expression of a marker protein having at least one portion which is displayed on the surface of a cell which expresses it may be detected without necessarily lysing the cell (*e.g.* using a labeled antibody which binds specifically with a cell-surface domain of the protein).

Expression of a marker of the invention may be assessed by any of a wide variety of well known methods for detecting expression of a transcribed nucleic acid or protein. Non-limiting examples of such methods include immunological methods for detection of secreted, cell-surface, cytoplasmic, or nuclear proteins, protein purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse transcription methods, and nucleic acid amplification methods.

In a preferred embodiment, expression of a marker is assessed using an antibody (*e.g.* a radio-labeled, chromophore-labeled, fluorophore-labeled, or enzyme-labeled antibody), an antibody derivative (*e.g.* an antibody conjugated with a substrate or with the protein or ligand of a protein-ligand pair {*e.g.* biotin-streptavidin}), or an

antibody fragment (*e.g.* a single-chain antibody, an isolated antibody hypervariable domain, etc.) which binds specifically with a marker protein or fragment thereof, including a marker protein which has undergone all or a portion of its normal post-translational modification.

In another preferred embodiment, expression of a marker is assessed by preparing mRNA/cDNA (*i.e.* a transcribed polynucleotide) from cells in a patient sample, and by hybridizing the mRNA/cDNA with a reference polynucleotide which is a complement of a marker nucleic acid, or a fragment thereof. cDNA can, optionally, be amplified using any of a variety of polymerase chain reaction methods prior to hybridization with the reference polynucleotide; preferably, it is not amplified. Expression of one or more markers can likewise be detected using quantitative PCR to assess the level of expression of the marker(s). Alternatively, any of the many known methods of detecting mutations or variants (*e.g.* single nucleotide polymorphisms, deletions, etc.) of a marker of the invention may be used to detect occurrence of a marker in a patient.

In a related embodiment, a mixture of transcribed polynucleotides obtained from the sample is contacted with a substrate having fixed thereto a polynucleotide complementary to or homologous with at least a portion (*e.g.* at least 7, 10, 15, 20, 25, 30, 40, 50, 100, 500, or more nucleotide residues) of a marker nucleic acid. If polynucleotides complementary to or homologous with are differentially detectable on the substrate (*e.g.* detectable using different chromophores or fluorophores, or fixed to different selected positions), then the levels of expression of a plurality of markers can be assessed simultaneously using a single substrate (*e.g.* a "gene chip" microarray of polynucleotides fixed at selected positions). When a method of assessing marker expression is used which involves hybridization of one nucleic acid with another, it is preferred that the hybridization be performed under stringent hybridization conditions.

Because the compositions, kits, and methods of the invention rely on detection of a difference in expression levels of one or more markers of the invention, it is preferable that the level of expression of the marker is significantly greater than the minimum detection limit of the method used to assess expression in at least one of normal cervical cells and cancerous cervical cells.

It is understood that by routine screening of additional patient samples using one or more of the markers of the invention, it will be realized that certain of the markers are over-expressed in cancers of various types, including specific cervical cancers, as well as other cancers such as breast cancer, ovarian cancer, etc. For example, it will be confirmed that some of the markers of the invention are over-expressed in most (*i.e.* 50% or more) or substantially all (*i.e.* 80% or more) of cervical cancer. Furthermore, it will be confirmed that certain of the markers of the invention are associated with cervical cancer of various stages (*i.e.* stage 0, I, II, III, and IV cervical cancers, as well as subclassifications IA1, IA2, IB, IB1, IB2, IIA, IIB, IIIA, IIIB, IVA, and IVB, using the FIGO Stage Grouping system for primary carcinoma of the cervix (see Gynecologic Oncology, 1991, 41:199 and Cancer, 1992, 69:482)), and pre-malignant conditions (*e.g.*, dysplasia including CIN or SIL), of various histologic subtypes (*e.g.* squamous cell carcinomas and squamous cell carcinoma variants such as verrucous carcinoma, lymphoepithelioma-like carcinoma, papillary squamous neoplasm and spindle cell squamous cell carcinoma (see Cervical Cancer and Preinvasive Neoplasia, 1996, pp. 90-91) serous, mucinous, endometrioid, and clear cell subtypes, as well as subclassifications and alternate classifications adenocarcinoma, papillary adenocarcinoma, papillary cystadenocarcinoma, surface papillary carcinoma, malignant adenofibroma, cystadenofibroma, adenocarcinoma, cystadenocarcinoma, adenoacanthoma, endometrioid stromal sarcoma, mesodermal {Müllerian} mixed tumor, malignant carcinoma, Brenner tumor, mixed epithelial tumor, and undifferentiated carcinoma, using the WHO/FIGO system for classification of malignant cervical tumors; Scully, *Atlas of Tumor Pathology*, 3d series, Washington DC), and various grades (*i.e.* grade I {well differentiated} , grade II {moderately well differentiated}, and grade III {poorly differentiated from surrounding normal tissue}). In addition, as a greater number of patient samples are assessed for expression of the markers of the invention and the outcomes of the individual patients from whom the samples were obtained are correlated, it will also be confirmed that altered expression of certain of the markers of the invention are strongly correlated with malignant cancers and that altered expression of other markers of the invention are strongly correlated with benign tumors. The compositions, kits, and methods of the invention are thus useful for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of cervical cancer in patients.

When the compositions, kits, and methods of the invention are used for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of cervical cancer in a patient, it is preferred that the marker or panel of markers of the invention is selected such that a positive result is obtained in at least about 20%, and preferably at least about 40%, 60%, or 80%, and more preferably in substantially all patients afflicted with a cervical cancer of the corresponding stage, grade, histological type, or benign/malignant nature. Preferably, the marker or panel of markers of the invention is selected such that a positive predictive value (PPV) of greater than about 10% is obtained for the general population (more preferably coupled with an assay specificity greater than 80%).

When a plurality of markers of the invention are used in the compositions, kits, and methods of the invention, the level of expression of each marker in a patient sample can be compared with the normal level of expression of each of the plurality of markers in non-cancerous samples of the same type, either in a single reaction mixture (*i.e.* using reagents, such as different fluorescent probes, for each marker) or in individual reaction mixtures corresponding to one or more of the markers. In one embodiment, a significantly increased level of expression of more than one of the plurality of markers in the sample, relative to the corresponding normal levels, is an indication that the patient is afflicted with cervical cancer. When a plurality of markers is used, it is preferred that 2, 3, 4, 5, 8, 10, 12, 15, 20, 30, or 50 or more individual markers be used, wherein fewer markers are preferred.

In order to maximize the sensitivity of the compositions, kits, and methods of the invention (*i.e.* by interference attributable to cells of non-cervical origin in a patient sample), it is preferable that the marker of the invention used therein be a marker which has a restricted tissue distribution, *e.g.*, normally not expressed in a non-cervical tissue.

Only a small number of markers are known to be associated with cervical cancer (*e.g.* bcl-2, 15A8 antigen, cdc6, Mcm5, and EGFR). These markers are not, of course, included among the markers of the invention, although they may be used together with one or more markers of the invention in a panel of markers, for example. It is well known that certain types of genes, such as oncogenes, tumor suppressor genes, growth factor-like genes, protease-like genes, and protein kinase-like genes are often involved with development of cancers of various types. Thus, among the markers of the

invention, use of those which correspond to proteins which resemble known proteins encoded by known oncogenes and tumor suppressor genes, and those which correspond to proteins which resemble growth factors, proteases, and protein kinases are preferred.

It is recognized that the compositions, kits, and methods of the invention will be of particular utility to patients having an enhanced risk of developing cervical cancer and their medical advisors. Patients recognized as having an enhanced risk of developing cervical cancer include, for example, patients having a familial history of cervical cancer, patients identified as having a mutant oncogene (*i.e.* at least one allele), and patients of advancing age (*i.e.* women older than about 50 or 60 years).

The level of expression of a marker in normal (*i.e.* non-cancerous) human cervical tissue can be assessed in a variety of ways. In one embodiment, this normal level of expression is assessed by assessing the level of expression of the marker in a portion of cervical cells which appears to be non-cancerous and by comparing this normal level of expression with the level of expression in a portion of the cervical cells which is suspected of being cancerous. Alternately, and particularly as further information becomes available as a result of routine performance of the methods described herein, population-average values for normal expression of the markers of the invention may be used. In other embodiments, the 'normal' level of expression of a marker may be determined by assessing expression of the marker in a patient sample obtained from a non-cancer-afflicted patient, from a patient sample obtained from a patient before the suspected onset of cervical cancer in the patient, from archived patient samples, and the like.

The invention includes compositions, kits, and methods for assessing the presence of cervical cancer cells in a sample (*e.g.* an archived tissue sample or a sample obtained from a patient). These compositions, kits, and methods are substantially the same as those described above, except that, where necessary, the compositions, kits, and methods are adapted for use with samples other than patient samples. For example, when the sample to be used is a parafinized, archived human tissue sample, it can be necessary to adjust the ratio of compounds in the compositions of the invention, in the kits of the invention, or the methods used to assess levels of marker expression in the sample. Such methods are well known in the art and within the skill of the ordinary artisan.

The invention includes a kit for assessing the presence of cervical cancer cells (*e.g.* in a sample such as a patient sample). The kit comprises a plurality of reagents, each of which is capable of binding specifically with a marker nucleic acid or protein. Suitable reagents for binding with a marker protein include antibodies, antibody derivatives, antibody fragments, and the like. Suitable reagents for binding with a marker nucleic acid (*e.g.* a genomic DNA, an mRNA, a spliced mRNA, a cDNA, or the like) include complementary nucleic acids. For example, the nucleic acid reagents may include oligonucleotides (labeled or non-labeled) fixed to a substrate, labeled oligonucleotides not bound with a substrate, pairs of PCR primers, molecular beacon probes, and the like.

The kit of the invention may optionally comprise additional components useful for performing the methods of the invention. By way of example, the kit may comprise fluids (*e.g.* SSC buffer) suitable for annealing complementary nucleic acids or for binding an antibody with a protein with which it specifically binds, one or more sample compartments, an instructional material which describes performance of a method of the invention, a sample of normal cervical cells, a sample of cervical cancer cells, and the like.

The invention also includes a method of making an isolated hybridoma which produces an antibody useful for assessing whether patient is afflicted with an cervical cancer. In this method, a protein or peptide comprising the entirety or a segment of a marker protein is synthesized or isolated (*e.g.* by purification from a cell in which it is expressed or by transcription and translation of a nucleic acid encoding the protein or peptide *in vivo* or *in vitro* using known methods). A vertebrate, preferably a mammal such as a mouse, rat, rabbit, or sheep, is immunized using the protein or peptide. The vertebrate may optionally (and preferably) be immunized at least one additional time with the protein or peptide, so that the vertebrate exhibits a robust immune response to the protein or peptide. Splenocytes are isolated from the immunized vertebrate and fused with an immortalized cell line to form hybridomas, using any of a variety of methods well known in the art. Hybridomas formed in this manner are then screened using standard methods to identify one or more hybridomas which produce an antibody which specifically binds with the marker protein or a fragment thereof. The invention also includes hybridomas made by this method and antibodies made using such hybridomas.

The invention also includes a method of assessing the efficacy of a test compound for inhibiting cervical cancer cells. As described above, differences in the level of expression of the markers of the invention correlate with the cancerous state of cervical cells. Although it is recognized that changes in the levels of expression of certain of the markers of the invention likely result from the cancerous state of cervical cells, it is likewise recognized that changes in the levels of expression of other of the markers of the invention induce, maintain, and promote the cancerous state of those cells. Thus, compounds which inhibit an cervical cancer in a patient will cause the level of expression of one or more of the markers of the invention to change to a level nearer the normal level of expression for that marker (*i.e.* the level of expression for the marker in non-cancerous cervical cells).

This method thus comprises comparing expression of a marker in a first cervical cell sample and maintained in the presence of the test compound and expression of the marker in a second cervical cell sample and maintained in the absence of the test compound. A significantly reduced expression of a marker of the invention in the presence of the test compound is an indication that the test compound inhibits cervical cancer. The cervical cell samples may, for example, be aliquots of a single sample of normal cervical cells obtained from a patient, pooled samples of normal cervical cells obtained from a patient, cells of a normal cervical cell line, aliquots of a single sample of cervical cancer cells obtained from a patient, pooled samples of cervical cancer cells obtained from a patient, cells of an cervical cancer cell line, or the like. In one embodiment, the samples are cervical cancer cells obtained from a patient and a plurality of compounds known to be effective for inhibiting various cervical cancers are tested in order to identify the compound which is likely to best inhibit the cervical cancer in the patient.

This method may likewise be used to assess the efficacy of a therapy for inhibiting cervical cancer in a patient. In this method, the level of expression of one or more markers of the invention in a pair of samples (one subjected to the therapy, the other not subjected to the therapy) is assessed. As with the method of assessing the efficacy of test compounds, if the therapy induces a significantly lower level of expression of a marker of the invention then the therapy is efficacious for inhibiting cervical cancer. As above, if samples from a selected patient are used in this method,

then alternative therapies can be assessed *in vitro* in order to select a therapy most likely to be efficacious for inhibiting cervical cancer in the patient.

As described above, the cancerous state of human cervical cells is correlated with changes in the levels of expression of the markers of the invention. The invention includes a method for assessing the human cervical cell carcinogenic potential of a test compound. This method comprises maintaining separate aliquots of human cervical cells in the presence and absence of the test compound. Expression of a marker of the invention in each of the aliquots is compared. A significantly higher level of expression of a marker of the invention in the aliquot maintained in the presence of the test compound (relative to the aliquot maintained in the absence of the test compound) is an indication that the test compound possesses human cervical cell carcinogenic potential. The relative carcinogenic potentials of various test compounds can be assessed by comparing the degree of enhancement or inhibition of the level of expression of the relevant markers, by comparing the number of markers for which the level of expression is enhanced or inhibited, or by comparing both.

Various aspects of the invention are described in further detail in the following subsections.

I. Isolated Nucleic Acid Molecules

One aspect of the invention pertains to isolated nucleic acid molecules, including nucleic acids which encode a marker protein or a portion thereof. Isolated nucleic acids of the invention also include nucleic acid molecules sufficient for use as hybridization probes to identify marker nucleic acid molecules, and fragments of marker nucleic acid molecules, *e.g.*, those suitable for use as PCR primers for the amplification or mutation of marker nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Preferably, an "isolated" nucleic acid molecule is free of sequences (preferably protein-encoding sequences) which naturally flank the nucleic acid (*i.e.*,

sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kB, 4 kB, 3 kB, 2 kB, 1 kB, 0.5 kB or 0.1 kB of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention can be isolated using standard molecular biology techniques and the sequence information in the database records described herein. Using all or a portion of such nucleic acid sequences, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook *et al.*, ed., *Molecular Cloning: A Laboratory Manual, 2nd ed.,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

A nucleic acid molecule of the invention can be amplified using cDNA, mRNA, or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, nucleotides corresponding to all or a portion of a nucleic acid molecule of the invention can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which has a nucleotide sequence complementary to the nucleotide sequence of a marker nucleic acid or to the nucleotide sequence of a nucleic acid encoding a marker protein. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence, wherein the full length nucleic acid sequence comprises a marker nucleic acid or which encodes a marker protein. Such nucleic acids

can be used, for example, as a probe or primer. The probe/primer typically is used as one or more substantially purified oligonucleotides. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 7, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 or more consecutive nucleotides of a nucleic acid of the invention.

Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences corresponding to one or more markers of the invention. The probe comprises a label group attached thereto, *e.g.*, a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as part of a diagnostic test kit for identifying cells or tissues which mis-express the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, *e.g.*, detecting mRNA levels or determining whether a gene encoding the protein has been mutated or deleted.

The invention further encompasses nucleic acid molecules that differ, due to degeneracy of the genetic code, from the nucleotide sequence of nucleic acids encoding a marker protein (*e.g.*, a protein having one of the amino acid sequences set forth in the Sequence Listing), and thus encode the same protein.

It will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequence can exist within a population (*e.g.*, the human population). Such genetic polymorphisms can exist among individuals within a population due to natural allelic variation. An allele is one of a group of genes which occur alternatively at a given genetic locus. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist that may affect the overall expression level of that gene (*e.g.*, by affecting regulation or degradation).

As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence.

As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a polypeptide corresponding to a marker of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be

readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

In another embodiment, an isolated nucleic acid molecule of the invention is at least 7, 15, 20, 25, 30, 40, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 550, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3500, 4000, 4500, or more nucleotides in length and hybridizes under stringent conditions to a marker nucleic acid or to a nucleic acid encoding a marker protein. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in sections 6.3.1-6.3.6 of *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989). A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C.

In addition to naturally-occurring allelic variants of a nucleic acid molecule of the invention that can exist in the population, the skilled artisan will further appreciate that sequence changes can be introduced by mutation thereby leading to changes in the amino acid sequence of the encoded protein, without altering the biological activity of the protein encoded thereby. For example, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are not conserved or only semi-conserved among homologs of various species may be non-essential for activity and thus would be likely targets for alteration. Alternatively, amino acid residues that are conserved among the homologs of various species (*e.g.*, murine and human) may be essential for activity and thus would not be likely targets for alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a variant marker protein that contain changes in amino acid residues that are not essential for activity. Such variant marker proteins differ in amino acid sequence from the naturally-occurring marker proteins, yet retain biological activity. In one embodiment, such a variant marker protein has an amino acid sequence that is at least about 40% identical, 50%, 60%, 70%, 80%, 90%, 95%, or 98% identical to the amino acid sequence of a marker protein.

An isolated nucleic acid molecule encoding a variant marker protein can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of marker nucleic acids, such that one or more amino acid residue substitutions, additions, or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), non-polar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

The present invention encompasses antisense nucleic acid molecules, *i.e.*, molecules which are complementary to a sense nucleic acid of the invention, *e.g.*, complementary to the coding strand of a double-stranded marker cDNA molecule or complementary to a marker mRNA sequence. Accordingly, an antisense nucleic acid of the invention can hydrogen bond to (*i.e.* anneal with) a sense nucleic acid of the invention. The antisense nucleic acid can be complementary to an entire coding strand,

or to only a portion thereof, *e.g.*, all or part of the protein coding region (or open reading frame). An antisense nucleic acid molecule can also be antisense to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding a marker protein. The non-coding regions ("5' and 3' untranslated regions") are the 5' and 3' sequences which flank the coding region and are not translated into amino acids.

An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 or more nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been sub-cloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a marker protein to thereby inhibit expression of the marker, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. Examples of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site or infusion of the antisense nucleic acid into an ovary-associated body fluid. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

An antisense nucleic acid molecule of the invention can be an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual α-units, the strands run parallel to each other (Gaultier *et al.,* 1987, *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.,* 1987, *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.,* 1987, *FEBS Lett.* 215:327-330).

The invention also encompasses ribozymes. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes as described in Haselhoff and Gerlach, 1988, *Nature* 334:585-591) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A ribozyme having specificity for a nucleic acid molecule encoding a marker protein can be designed based

upon the nucleotide sequence of a cDNA corresponding to the marker. For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved (see Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742). Alternatively, an mRNA encoding a polypeptide of the invention can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, *e.g.*, Bartel and Szostak, 1993, *Science* 261:1411-1418).

The invention also encompasses nucleic acid molecules which form triple helical structures. For example, expression of a marker of the invention can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the marker nucleic acid or protein (*e.g.*, the promoter and/or enhancer) to form triple helical structures that prevent transcription of the gene in target cells. See generally Helene (1991) *Anticancer Drug Des.* 6(6):569-84; Helene (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher (1992) *Bioassays* 14(12):807-15.

In various embodiments, the nucleic acid molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup *et al.*, 1996, *Bioorganic & Medicinal Chemistry* 4(1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup *et al.* (1996), *supra*; Perry-O'Keefe *et al.* (1996) *Proc. Natl. Acad. Sci. USA* 93:14670-675.

PNAs can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, *e.g.*, inducing transcription or translation arrest or inhibiting replication. PNAs can also be used, *e.g.*, in the analysis of single base pair mutations in a gene by, *e.g.*, PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, *e.g.*, S1 nucleases (Hyrup

(1996), *supra*; or as probes or primers for DNA sequence and hybridization (Hyrup, 1996, *supra*; Perry-O'Keefe *et al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:14670-675).

In another embodiment, PNAs can be modified, *e.g.*, to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated which can combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, *e.g.*, RNase H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup, 1996, *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), *supra,* and Finn *et al.* (1996) *Nucleic Acids Res.* 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag *et al.*, 1989, *Nucleic Acids Res.* 17:5973-88). PNA monomers are then coupled in a step-wise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn *et al.*, 1996, *Nucleic Acids Res.* 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser *et al.*, 1975, *Bioorganic Med. Chem. Lett.* 5:1119-11124).

In other embodiments, the oligonucleotide can include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre *et al.*, 1987, *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. WO 88/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, 1988, *Bio/Techniques* 6:958-976) or intercalating agents (see, *e.g.*, Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The invention also includes molecular beacon nucleic acids having at least one region which is complementary to a nucleic acid of the invention, such that the molecular beacon is useful for quantitating the presence of the nucleic acid of the invention in a sample. A "molecular beacon" nucleic acid is a nucleic acid comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid are not annealed with one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acids are described, for example, in U.S. Patent 5,876,930.

II. Isolated Proteins and Antibodies

One aspect of the invention pertains to isolated marker proteins and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a marker protein or a fragment thereof. In one embodiment, the native marker protein can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, a protein or peptide comprising the whole or a segment of the marker protein is produced by recombinant DNA techniques. Alternative to recombinant expression, such protein or peptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less

than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

Biologically active portions of a marker protein include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the marker protein, which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding full-length protein. A biologically active portion of a marker protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the marker protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of the marker protein.

Preferred marker proteins are encoded by nucleotide sequences comprising the sequence of any of the sequences set forth in the Sequence Listing. Other useful proteins are substantially identical (*e.g.*, at least about 40%, preferably 50%, 60%, 70%, 80%, 90%, 95%, or 99%) to one of these sequences and retain the functional activity of the corresponding naturally-occurring marker protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, %

identity = # of identical positions/total # of positions (*e.g.*, overlapping positions) x100). In one embodiment the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the BLASTN and BLASTX programs of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with the BLASTN program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTP program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, a newer version of the BLAST algorithm called Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402, which is able to perform gapped local alignments for the programs BLASTN, BLASTP and BLASTX. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (*e.g.*, BLASTX and BLASTN) can be used. See http://www.ncbi.nlm.nih.gov. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85:2444-2448. When using the FASTA algorithm for comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a *k*-tuple value of 2.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

The invention also provides chimeric or fusion proteins comprising a marker protein or a segment thereof. As used herein, a "chimeric protein" or "fusion protein" comprises all or part (preferably a biologically active part) of a marker protein operably linked to a heterologous polypeptide (*i.e.*, a polypeptide other than the marker protein). Within the fusion protein, the term "operably linked" is intended to indicate that the marker protein or segment thereof and the heterologous polypeptide are fused in-frame to each other. The heterologous polypeptide can be fused to the amino-terminus or the carboxyl-terminus of the marker protein or segment.

One useful fusion protein is a GST fusion protein in which a marker protein or segment is fused to the carboxyl terminus of GST sequences. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

In another embodiment, the fusion protein contains a heterologous signal sequence at its amino terminus. For example, the native signal sequence of a marker protein can be removed and replaced with a signal sequence from another protein. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence (Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, 1992). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of melittin and human placental alkaline phosphatase (Stratagene; La Jolla, California). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook *et al., supra*) and the protein A secretory signal (Pharmacia Biotech; Piscataway, New Jersey).

In yet another embodiment, the fusion protein is an immunoglobulin fusion protein in which all or part of a marker protein is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand (soluble or membrane-bound) and a protein on the surface of a cell (receptor), to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion protein can be used to affect the bioavailability of a cognate ligand of a marker protein. Inhibition of ligand/receptor interaction can be

useful therapeutically, both for treating proliferative and differentiative disorders and for modulating (*e.g.* promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies directed against a marker protein in a subject, to purify ligands and in screening assays to identify molecules which inhibit the interaction of the marker protein with ligands.

Chimeric and fusion proteins of the invention can be produced by standard recombinant DNA techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see, *e.g.*, Ausubel *et al.*, *supra*). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A nucleic acid encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide of the invention.

A signal sequence can be used to facilitate secretion and isolation of marker proteins. Signal sequences are typically characterized by a core of hydrophobic amino acids which are generally cleaved from the mature protein during secretion in one or more cleavage events. Such signal peptides contain processing sites that allow cleavage of the signal sequence from the mature proteins as they pass through the secretory pathway. Thus, the invention pertains to marker proteins, fusion proteins or segments thereof having a signal sequence, as well as to such proteins from which the signal sequence has been proteolytically cleaved (*i.e.*, the cleavage products). In one embodiment, a nucleic acid sequence encoding a signal sequence can be operably linked in an expression vector to a protein of interest, such as a marker protein or a segment thereof. The signal sequence directs secretion of the protein, such as from a eukaryotic host into which the expression vector is transformed, and the signal sequence is subsequently or concurrently cleaved. The protein can then be readily purified from the extracellular medium by art recognized methods. Alternatively, the signal sequence can be linked to the protein of interest using a sequence which facilitates purification, such as with a GST domain.

The present invention also pertains to variants of the marker proteins. Such variants have an altered amino acid sequence which can function as either agonists (mimetics) or as antagonists. Variants can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation. An agonist can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of the protein. An antagonist of a protein can inhibit one or more of the activities of the naturally occurring form of the protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the protein of interest. Thus, specific biological effects can be elicited by treatment with a variant of limited function. Treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein can have fewer side effects in a subject relative to treatment with the naturally occurring form of the protein.

Variants of a marker protein which function as either agonists (mimetics) or as antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of the protein of the invention for agonist or antagonist activity. In one embodiment, a variegated library of variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential protein sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display). There are a variety of methods which can be used to produce libraries of potential variants of the marker proteins from a degenerate oligonucleotide sequence. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, 1983, *Tetrahedron* 39:3; Itakura *et al.*, 1984, *Annu. Rev. Biochem.* 53:323; Itakura *et al.*, 1984, *Science* 198:1056; Ike *et al.*, 1983 *Nucleic Acid Res.* 11:477).

In addition, libraries of segments of a marker protein can be used to generate a variegated population of polypeptides for screening and subsequent selection of variant marker proteins or segments thereof. For example, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of the coding sequence of interest with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different

nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes amino terminal and internal fragments of various sizes of the protein of interest.

Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify variants of a protein of the invention (Arkin and Yourvan, 1992, *Proc. Natl. Acad. Sci. USA* *89*:7811-7815; Delgrave *et al.,* 1993, *Protein Engineering* 6(3):327- 331).

Another aspect of the invention pertains to antibodies directed against a protein of the invention. In preferred embodiments, the antibodies specifically bind a marker protein or a fragment thereof. The terms "antibody" and "antibodies" as used interchangeably herein refer to immunoglobulin molecules as well as fragments and derivatives thereof that comprise an immunologically active portion of an immunoglobulin molecule, (*i.e.*, such a portion contains an antigen binding site which specifically binds an antigen, such as a marker protein, *e.g.*, an epitope of a marker protein). An antibody which specifically binds to a protein of the invention is an antibody which binds the protein, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the protein. Examples of an immunologically active portion of an immunoglobulin molecule include, but are not limited to, single-chain antibodies (scAb), F(ab) and $F(ab')_2$ fragments.

An isolated protein of the invention or a fragment thereof can be used as an immunogen to generate antibodies. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. The antigenic peptide of a protein of the invention comprises at least 8 (preferably 10, 15, 20, or 30 or more) amino acid residues of the amino acid sequence of one of the

proteins of the invention, and encompasses at least one epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with the protein. Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, *e.g.*, hydrophilic regions. Hydrophobicity sequence analysis, hydrophilicity sequence analysis, or similar analyses can be used to identify hydrophilic regions. In preferred embodiments, an isolated marker protein or fragment thereof is used as an immunogen.

An immunogen typically is used to prepare antibodies by immunizing a suitable (*i.e.* immunocompetent) subject such as a rabbit, goat, mouse, or other mammal or vertebrate. An appropriate immunogenic preparation can contain, for example, recombinantly-expressed or chemically-synthesized protein or peptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or a similar immunostimulatory agent. Preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made using a non-human host cell for recombinant expression of a protein of the invention. In such a manner, the resulting antibody compositions have reduced or no binding of human proteins other than a protein of the invention.

The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope. Preferred polyclonal and monoclonal antibody compositions are ones that have been selected for antibodies directed against a protein of the invention. Particularly preferred polyclonal and monoclonal antibody preparations are ones that contain only antibodies directed against a marker protein or fragment thereof.

Polyclonal antibodies can be prepared by immunizing a suitable subject with a protein of the invention as an immunogen The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. At an appropriate time after immunization, *e.g.*, when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies (mAb) by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell

hybridoma technique (see Kozbor *et al.,* 1983, *Immunol. Today* 4:72), the EBV-hybridoma technique (see Cole *et al.*, pp. 77-96 In *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., 1985) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology,* Coligan *et al.* ed., John Wiley & Sons, New York, 1994). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, *e.g.*, using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a protein of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System,* Catalog No. 27-9400-01; and the Stratagene *SurfZAP Phage Display Kit,* Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275- 1281; Griffiths *et al.* (1993) *EMBO J.* 12:725-734.

The invention also provides recombinant antibodies that specifically bind a protein of the invention. In preferred embodiments, the recombinant antibodies specifically binds a marker protein or fragment thereof. Recombinant antibodies include, but are not limited to, chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, single-chain antibodies and multi-specific antibodies. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, *e.g.,* Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Single-chain antibodies have an

antigen binding site and consist of a single polypeptide. They can be produced by techniques known in the art, for example using methods described in Ladner *et. al* U.S. Pat. No. 4,946,778 (which is incorporated herein by reference in its entirety); Bird *et al.*, (1988) *Science* 242:423-426; Whitlow *et al.*, (1991) *Methods in Enzymology* 2:1-9; Whitlow *et al.*, (1991) *Methods in Enzymology* 2:97-105; and Huston *et al.*, (1991) *Methods in Enzymology Molecular Design and Modeling: Concepts and Applications* 203:46-88. Multi-specific antibodies are antibody molecules having at least two antigen-binding sites that specifically bind different antigens. Such molecules can be produced by techniques known in the art, for example using methods described in Segal, U.S. Patent No. 4,676,980 (the disclosure of which is incorporated herein by reference in its entirety); Holliger et al., (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; *Whitlow et al.*, (1994) *Protein Eng.* 7:1017-1026 and U.S. Pat. No. 6,121,424.

Humanized antibodies are antibody molecules from non-human species having one or more complementarity determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, *e.g.*, Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521- 3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Cancer Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; and Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559); Morrison (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

More particularly, humanized antibodies can be produced, for example, using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of a polypeptide corresponding to a marker of the invention. Monoclonal

antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995) *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, *e.g.*, U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, *e.g.*, a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope (Jespers *et al.,* 1994, *Bio/technology* 12:899-903).

The antibodies of the invention can be isolated after production (*e.g.*, from the blood or serum of the subject) or synthesis and further purified by well-known techniques. For example, IgG antibodies can be purified using protein A chromatography. Antibodies specific for a protein of the invention can be selected or (*e.g.*, partially purified) or purified by, *e.g.*, affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, *i.e.,* one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those of the desired protein of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is

contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein of the invention.

In a preferred embodiment, the substantially purified antibodies of the invention may specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain or cytoplasmic membrane of a protein of the invention. In a particularly preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a protein of the invention. In a more preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a marker protein.

An antibody directed against a protein of the invention can be used to isolate the protein by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, such an antibody can be used to detect the marker protein or fragment thereof (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the level and pattern of expression of the marker. The antibodies can also be used diagnostically to monitor protein levels in tissues or body fluids (*e.g.* in a cervical-associated body fluid) as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by the use of an antibody derivative, which comprises an antibody of the invention coupled to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

Antibodies of the invention may also be used as therapeutic agents in treating cancers. In a preferred embodiment, completely human antibodies of the invention are used for therapeutic treatment of human cancer patients, particularly those having an cervical cancer. In another preferred embodiment, antibodies that bind specifically to a marker protein or fragment thereof are used for therapeutic treatment. Further, such therapeutic antibody may be an antibody derivative or immunotoxin comprising an antibody conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

The conjugated antibodies of the invention can be used for modifying a given biological response, for the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as ribosome-inhibiting protein (see Better et al., U.S. Patent No. 6,146,631, the disclosure of which is incorporated herein in its entirety), abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, .alpha.-interferon, .beta.-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophase colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982).

Accordingly, in one aspect, the invention provides substantially purified antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. In various embodiments, the substantially purified antibodies of the invention, or fragments or derivatives thereof, can be human, non-human, chimeric and/or humanized antibodies. In another aspect, the invention provides non-human antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. Such non-human antibodies can be goat, mouse, sheep, horse, chicken, rabbit, or rat antibodies. Alternatively, the non-human antibodies of the invention can be chimeric and/or humanized antibodies. In addition, the non-human antibodies of the invention can be polyclonal antibodies or monoclonal antibodies. In still a further aspect, the invention provides monoclonal antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. The monoclonal antibodies can be human, humanized, chimeric and/or non-human antibodies.

The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the invention is a pharmaceutical composition comprising an antibody of the invention. In one embodiment, the pharmaceutical composition comprises an antibody of the invention and a pharmaceutically acceptable carrier.

III. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a marker protein (or a portion of such a protein). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, namely expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids (vectors). However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, *Methods in Enzymology: Gene Expression Technology* vol.185, Academic Press, San Diego, CA (1991). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and

those which direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

The recombinant expression vectors of the invention can be designed for expression of a marker protein or a segment thereof in prokaryotic (*e.g.*, *E. coli*) or eukaryotic cells (*e.g.*, insect cells {using baculovirus expression vectors}, yeast cells or mammalian cells). Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988, *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, 1988, *Gene* 69:301-315) and pET 11d (Studier *et al.*, p. 60-89, In *Gene Expression Technology: Methods in Enzymology* vol.185, Academic Press, San Diego, CA, 1991). Target gene expression from the pTrc vector relies on host RNA

polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a co-expressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, p. 119-128, In *Gene Expression Technology: Methods in Enzymology* vol. 185, Academic Press, San Diego, CA, 1990. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al.,* 1992, *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari *et al.,* 1987, *EMBO J.* 6:229-234), pMFa (Kurjan and Herskowitz, 1982, *Cell* 30:933-943), pJRY88 (Schultz *et al.,* 1987, *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and pPicZ (Invitrogen Corp, San Diego, CA).

Alternatively, the expression vector is a baculovirus expression vector. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, Sf 9 cells) include the pAc series (Smith *et al.*, 1983, *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers, 1989, *Virology* 170:31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987, *Nature* 329:840) and pMT2PC (Kaufman *et al.,* 1987, *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook *et al.*, *supra.*

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert *et al.,* 1987, *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton, 1988, *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989, *EMBO J.* 8:729-733) and immunoglobulins (Banerji *et al.,* 1983, *Cell* 33:729-740; Queen and Baltimore, 1983, *Cell* 33:741-748), neuron-specific promoters (*e.g.*, the neurofilament promoter; Byrne and Ruddle, 1989, *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund *et al.,* 1985, *Science* 230:912-916), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss, 1990, *Science* 249:374-379) and the α-fetoprotein promoter (Camper and Tilghman, 1989, *Genes Dev.* 3:537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operably linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to the mRNA encoding a polypeptide of the invention. Regulatory sequences operably linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue-specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub *et al.,* 1986, *Trends in Genetics,* Vol. 1(1).

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic (*e.g.*, *E. coli*) or eukaryotic cell (*e.g.*, insect cells, yeast or mammalian cells).

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce a marker protein or a segment thereof. Accordingly, the invention further provides methods for producing a marker protein or a segment thereof using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a marker protein or a segment thereof has been introduced) in a suitable medium such that the is produced. In another embodiment, the method further

comprises isolating the marker protein or a segment thereof from the medium or the host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a sequences encoding a marker protein or a segment thereof have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous sequences encoding a marker protein of the invention have been introduced into their genome or homologous recombinant animals in which endogenous gene(s) encoding a marker protein have been altered. Such animals are useful for studying the function and/or activity of the marker protein and for identifying and/or evaluating modulators of marker protein. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing a nucleic acid encoding a marker protein into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the polypeptide of the invention to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No.

4,873,191 and in Hogan, *Manipulating the Mouse Embryo*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of mRNA encoding the transgene in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying the transgene can further be bred to other transgenic animals carrying other transgenes.

To create an homologous recombinant animal, a vector is prepared which contains at least a portion of a gene encoding a marker protein into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous protein). In the homologous recombination vector, the altered portion of the gene is flanked at its 5' and 3' ends by additional nucleic acid of the gene to allow for homologous recombination to occur between the exogenous gene carried by the vector and an endogenous gene in an embryonic stem cell. The additional flanking nucleic acid sequences are of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see, *e.g.,* Thomas and Capecchi, 1987, *Cell* 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced gene has homologously recombined with the endogenous gene are selected (see, *e.g.,* Li *et al.,* 1992, *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see, *e.g.,* Bradley, *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, Ed., IRL, Oxford, 1987, pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed

animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication NOS. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, *e.g.*, Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.,* 1991, *Science* 251:1351-1355). If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.* (1997) *Nature* 385:810-813 and PCT Publication NOS. WO 97/07668 and WO 97/07669.

IV. Pharmaceutical Compositions

The nucleic acid molecules, polypeptides, and antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is

contemplated. Supplementary active compounds can also be incorporated into the compositions.

The invention includes methods for preparing pharmaceutical compositions for modulating the expression or activity of a marker nucleic acid or protein . Such methods comprise formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein. Such compositions can further include additional active agents. Thus, the invention further includes methods for preparing a pharmaceutical composition by formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein and one or more additional active compounds.

The invention also provides methods (also referred to herein as "screening assays") for identifying modulators, *i.e.,* candidate or test compounds or agents (*e.g.,* peptides, peptidomimetics, peptoids, small molecules or other drugs) which (a) bind to the marker, or (b) have a modulatory (*e.g.,* stimulatory or inhibitory) effect on the activity of the marker or, more specifically, (c) have a modulatory effect on the interactions of the marker with one or more of its natural substrates (*e.g.,* peptide, protein, hormone, co-factor, or nucleic acid), or (d) have a modulatory effect on the expression of the marker. Such assays typically comprise a reaction between the marker and one or more assay components. The other components may be either the test compound itself, or a combination of test compound and a natural binding partner of the marker.

The test compounds of the present invention may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. Test compounds may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, *e.g.,* Zuckermann *et al.*, 1994, *J. Med. Chem.* 37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while

the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria and/or spores, (Ladner, USP 5,223,409), plasmids (Cull *et al*, 1992, *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla *et al*, 1990, *Proc. Natl. Acad. Sci.* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; Ladner, *supra.*).

In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a protein encoded by or corresponding to a marker or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to a protein encoded by or corresponding to a marker or biologically active portion thereof. Determining the ability of the test compound to directly bind to a protein can be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound to the marker can be determined by detecting the labeled marker compound in a complex. For example, compounds (*e.g.*, marker substrates) can be labeled with ^{125}I, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, assay components can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

In another embodiment, the invention provides assays for screening candidate or test compounds which modulate the expression of a marker or the activity of a protein encoded by or corresponding to a marker, or a biologically active portion

thereof. In all likelihood, the protein encoded by or corresponding to the marker can, *in vivo*, interact with one or more molecules, such as but not limited to, peptides, proteins, hormones, cofactors and nucleic acids. For the purposes of this discussion, such cellular and extracellular molecules are referred to herein as “binding partners” or marker “substrate”.

One necessary embodiment of the invention in order to facilitate such screening is the use of a protein encoded by or corresponding to marker to identify the protein’s natural *in vivo* binding partners. There are many ways to accomplish this which are known to one skilled in the art. One example is the use of the marker protein as "bait protein" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al*, 1993, *Cell* 72:223-232; Madura *et al*, 1993, *J. Biol. Chem.* 268:12046-12054; Bartel *et al* ,1993, *Biotechniques* 14:920-924; Iwabuchi *et al*, 1993 *Oncogene* 8:1693-1696; Brent WO94/10300) in order to identify other proteins which bind to or interact with the marker (binding partners) and, therefore, are possibly involved in the natural function of the marker. Such marker binding partners are also likely to be involved in the propagation of signals by the marker protein or downstream elements of a marker protein-mediated signaling pathway. Alternatively, such marker protein binding partners may also be found to be inhibitors of the marker protein.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that encodes a marker protein fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a marker-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be readily detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the marker protein.

In a further embodiment, assays may be devised through the use of the invention for the purpose of identifying compounds which modulate (*e.g.,* affect either positively or negatively) interactions between a marker protein and its substrates and/or binding partners. Such compounds can include, but are not limited to, molecules such as antibodies, peptides, hormones, oligonucleotides, nucleic acids, and analogs thereof. Such compounds may also be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. The preferred assay components for use in this embodiment is an cervical cancer marker protein identified herein, the known binding partner and/or substrate of same, and the test compound. Test compounds can be supplied from any source.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the marker protein and its binding partner involves preparing a reaction mixture containing the marker protein and its binding partner under conditions and for a time sufficient to allow the two products to interact and bind, thus forming a complex. In order to test an agent for inhibitory activity, the reaction mixture is prepared in the presence and absence of the test compound. The test compound can be initially included in the reaction mixture, or can be added at a time subsequent to the addition of the marker protein and its binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The formation of any complexes between the marker protein and its binding partner is then detected. The formation of a complex in the control reaction, but less or no such formation in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the marker protein and its binding partner. Conversely, the formation of more complex in the presence of compound than in the control reaction indicates that the compound may enhance interaction of the marker protein and its binding partner.

The assay for compounds that interfere with the interaction of the marker protein with its binding partner may be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the marker protein or its binding partner onto a solid phase and detecting complexes anchored to the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds

that interfere with the interaction between the marker proteins and the binding partners (*e.g.*, by competition) can be identified by conducting the reaction in the presence of the test substance, *i.e.*, by adding the test substance to the reaction mixture prior to or simultaneously with the marker and its interactive binding partner. Alternatively, test compounds that disrupt preformed complexes, *e.g.*, compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are briefly described below.

In a heterogeneous assay system, either the marker protein or its binding partner is anchored onto a solid surface or matrix, while the other corresponding non-anchored component may be labeled, either directly or indirectly. In practice, microtitre plates are often utilized for this approach. The anchored species can be immobilized by a number of methods, either non-covalent or covalent, that are typically well known to one who practices the art. Non-covalent attachment can often be accomplished simply by coating the solid surface with a solution of the marker protein or its binding partner and drying. Alternatively, an immobilized antibody specific for the assay component to be anchored can be used for this purpose. Such surfaces can often be prepared in advance and stored.

In related embodiments, a fusion protein can be provided which adds a domain that allows one or both of the assay components to be anchored to a matrix. For example, glutathione-S-transferase/marker fusion proteins or glutathione-S-transferase/binding partner can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, which are then combined with the test compound or the test compound and either the non-adsorbed marker or its binding partner, and the mixture incubated under conditions conducive to complex formation (*e.g.*, physiological conditions). Following incubation, the beads or microtiter plate wells are washed to remove any unbound assay components, the immobilized complex assessed either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of marker binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a marker protein or a marker protein binding partner can be immobilized utilizing conjugation of biotin and

streptavidin. Biotinylated marker protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the protein-immobilized surfaces can be prepared in advance and stored.

In order to conduct the assay, the corresponding partner of the immobilized assay component is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted assay components are removed (*e.g.*, by washing) and any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the non-immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; *e.g.*, using a labeled antibody specific for the initially non-immobilized species (the antibody, in turn, can be directly labeled or indirectly labeled with, *e.g.*, a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which modulate (inhibit or enhance) complex formation or which disrupt preformed complexes can be detected.

In an alternate embodiment of the invention, a homogeneous assay may be used. This is typically a reaction, analogous to those mentioned above, which is conducted in a liquid phase in the presence or absence of the test compound. The formed complexes are then separated from unreacted components, and the amount of complex formed is determined. As mentioned for heterogeneous assay systems, the order of addition of reactants to the liquid phase can yield information about which test compounds modulate (inhibit or enhance) complex formation and which disrupt preformed complexes.

In such a homogeneous assay, the reaction products may be separated from unreacted assay components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, complexes of molecules may be separated from uncomplexed molecules through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., *Trends Biochem Sci* 1993

Aug;18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the complex as compared to the uncomplexed molecules may be exploited to differentially separate the complex from the remaining individual reactants, for example through the use of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, *e.g.,* Heegaard, 1998, *J Mol. Recognit.* 11:141-148; Hage and Tweed, 1997, *J. Chromatogr. B. Biomed. Sci. Appl.,* 699:499-525). Gel electrophoresis may also be employed to separate complexed molecules from unbound species (see, *e.g.,* Ausubel *et al* (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, nondenaturing gels in the absence of reducing agent are typically preferred, but conditions appropriate to the particular interactants will be well known to one skilled in the art. Immunoprecipitation is another common technique utilized for the isolation of a protein-protein complex from solution (see, *e.g.,* Ausubel *et al* (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, all proteins binding to an antibody specific to one of the binding molecules are precipitated from solution by conjugating the antibody to a polymer bead that may be readily collected by centrifugation. The bound assay components are released from the beads (through a specific proteolysis event or other technique well known in the art which will not disturb the protein-protein interaction in the complex), and a second immunoprecipitation step is performed, this time utilizing antibodies specific for the correspondingly different interacting assay component. In this manner, only formed complexes should remain attached to the beads. Variations in complex formation in both the presence and the absence of a test compound can be compared, thus offering information about the ability of the compound to modulate interactions between the marker protein and its binding partner.

Also within the scope of the present invention are methods for direct detection of interactions between the marker protein and its natural binding partner and/or a test compound in a homogeneous or heterogeneous assay system without further sample manipulation. For example, the technique of fluorescence energy transfer may be utilized (see, *e.g.*, Lakowicz *et al*, U.S. Patent No. 5,631,169; Stavrianopoulos *et al*, U.S. Patent No. 4,868,103). Generally, this technique involves the addition of a fluorophore label on a first 'donor' molecule (*e.g.*, marker or test compound) such that its emitted fluorescent energy will be absorbed by a fluorescent label on a second, 'acceptor' molecule (*e.g.*, marker or test compound), which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter). A test substance which either enhances or hinders participation of one of the species in the preformed complex will result in the generation of a signal variant to that of background. In this way, test substances that modulate interactions between a marker and its binding partner can be identified in controlled assays.

In another embodiment, modulators of marker expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of marker mRNA or protein in the cell, is determined. The level of expression of marker mRNA or protein in the presence of the candidate compound is compared to the level of expression of marker mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of marker expression based on this comparison. For example, when expression of marker mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of marker mRNA or protein expression. Conversely, when expression of marker mRNA or protein is less (statistically significantly less) in the presence of the candidate compound

than in its absence, the candidate compound is identified as an inhibitor of marker mRNA or protein expression. The level of marker mRNA or protein expression in the cells can be determined by methods described herein for detecting marker mRNA or protein.

In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a marker protein can be further confirmed *in vivo*, *e.g.*, in a whole animal model for cellular transformation and/or tumorigenesis.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a marker modulating agent, an antisense marker nucleic acid molecule, a marker-specific antibody, or a marker-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

It is understood that appropriate doses of small molecule agents and protein or polypeptide agents depends upon a number of factors within the knowledge of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of these agents will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the agent to have upon the nucleic acid or polypeptide of the invention. Exemplary doses of a small molecule include milligram or microgram amounts per kilogram of subject or sample weight (*e.g.* about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram). Exemplary doses of a protein or polypeptide include gram, milligram or microgram amounts per kilogram of subject or sample weight (*e.g.* about 1 microgram per kilogram to about 5 grams per kilogram, about 100 micrograms per kilogram to about 500 milligrams per kilogram, or

about 1 milligram per kilogram to about 50 milligrams per kilogram). It is furthermore understood that appropriate doses of one of these agents depend upon the potency of the agent with respect to the expression or activity to be modulated. Such appropriate doses can be determined using the assays described herein. When one or more of these agents is to be administered to an animal (*e.g.* a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher can, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific agent employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediamine-tetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF; Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy

syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, a polypeptide or antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium, and then incorporating the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed.

Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches, and the like can contain any of the following ingredients, or compounds of a similar nature: a

binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes having monoclonal antibodies incorporated therein or thereon) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the

subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

For antibodies, the preferred dosage is 0.1 mg/kg to 100 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg). If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is usually appropriate. Generally, partially human antibodies and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (*e.g.*, into the cervical epithelium). A method for lipidation of antibodies is described by Cruikshank *et al.* (1997) *J. Acquired Immune Deficiency Syndromes and Human Retrovirology* 14:193.

The invention also provides vaccine compositions for the prevention and/or treatment of cervical cancer. The invention provides cervical cancer vaccine compositions in which a protein of a marker of Table 1, or a combination of proteins of the markers of Table 1, are introduced into a subject in order to stimulate an immune response against the cervical cancer. The invention also provides cervical cancer vaccine compositions in which a gene expression construct, which expresses a marker or fragment of a marker identified in Table 1, is introduced into the subject such that a protein or fragment of a protein encoded by a marker of Table 1 is produced by transfected cells in the subject at a higher than normal level and elicits an immune response.

In one embodiment, a cervical cancer vaccine is provided and employed as an immunotherapeutic agent for the prevention of cervical cancer. In another embodiment, a cervical cancer vaccine is provided and employed as an immunotherapeutic agent for the treatment of cervical cancer.

By way of example, a cervical cancer vaccine comprised of the proteins of the markers of Table 1, may be employed for the prevention and/or treatment of cervical cancer in a subject by administering the vaccine by a variety of routes, *e.g.*, intradermally, subcutaneously, or intramuscularly. In addition, the cervical cancer

vaccine can be administered together with adjuvants and/or immunomodulators to boost the activity of the vaccine and the subject's response. In one embodiment, devices and/or compositions containing the vaccine, suitable for sustained or intermittent release could be, implanted in the body or topically applied thereto for the relatively slow release of such materials into the body. The cervical cancer vaccine can be introduced along with immunomodulatory compounds, which can alter the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

In another embodiment, a cervical cancer vaccine comprised of an expression construct of the markers of Table 1, may be introduced by injection into muscle or by coating onto microprojectiles and using a device designed for the purpose to fire the projectiles at high speed into the skin. The cells of the subject will then express the protein(s) or fragments of proteins of the markers of Table 1 and induce an immune response. In addition, the cervical cancer vaccine may be introduced along with expression constructs for immunomodulatory molecules, such as cytokines, which may increase the immune response or modulate the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

The marker nucleic acid molecules can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470), or by stereotactic injection (see, *e.g.*, Chen *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.* retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

V. Predictive Medicine

The present invention pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trails are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining the level of expression of one or more marker proteins or nucleic acids, in order to determine whether an individual is at risk of developing cervical cancer. Such assays can be used for prognostic or predictive purposes to thereby prophylactically treat an individual prior to the onset of the cancer.

Yet another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs or other compounds administered either to inhibit cervical cancer or to treat or prevent any other disorder {*i.e.* in order to understand any cervical carcinogenic effects that such treatment may have}) on the expression or activity of a marker of the invention in clinical trials. These and other agents are described in further detail in the following sections.

A. Diagnostic Assays

An exemplary method for detecting the presence or absence of a marker protein or nucleic acid in a biological sample involves obtaining a biological sample (*e.g.* a cervical-associated body fluid) from a test subject and contacting the biological sample with a compound or an agent capable of detecting the polypeptide or nucleic acid (*e.g.*, mRNA, genomic DNA, or cDNA). The detection methods of the invention can thus be used to detect mRNA, protein, cDNA, or genomic DNA, for example, in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of a marker protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein or fragment thereof. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

A general principle of such diagnostic and prognostic assays involves preparing a sample or reaction mixture that may contain a marker, and a probe, under appropriate conditions and for a time sufficient to allow the marker and probe to interact and bind, thus forming a complex that can be removed and/or detected in the reaction mixture. These assays can be conducted in a variety of ways.

For example, one method to conduct such an assay would involve anchoring the marker or probe onto a solid phase support, also referred to as a substrate, and detecting target marker/probe complexes anchored on the solid phase at the end of the reaction. In one embodiment of such a method, a sample from a subject, which is to be assayed for presence and/or concentration of marker, can be anchored onto a carrier or solid phase support. In another embodiment, the reverse situation is possible, in which the probe can be anchored to a solid phase and a sample from a subject can be allowed to react as an unanchored component of the assay.

There are many established methods for anchoring assay components to a solid phase. These include, without limitation, marker or probe molecules which are immobilized through conjugation of biotin and streptavidin. Such biotinylated assay components can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the surfaces with immobilized assay components can be prepared in advance and stored.

Other suitable carriers or solid phase supports for such assays include any material capable of binding the class of molecule to which the marker or probe belongs. Well-known supports or carriers include, but are not limited to, glass, polystyrene, nylon, polypropylene, nylon, polyethylene, dextran, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

In order to conduct assays with the above mentioned approaches, the non-immobilized component is added to the solid phase upon which the second component is anchored. After the reaction is complete, uncomplexed components may be removed (*e.g.*, by washing) under conditions such that any complexes formed will remain immobilized upon the solid phase. The detection of marker/probe complexes anchored to the solid phase can be accomplished in a number of methods outlined herein.

In a preferred embodiment, the probe, when it is the unanchored assay component, can be labeled for the purpose of detection and readout of the assay, either directly or indirectly, with detectable labels discussed herein and which are well-known to one skilled in the art.

It is also possible to directly detect marker/probe complex formation without further manipulation or labeling of either component (marker or probe), for example by utilizing the technique of fluorescence energy transfer (see, for example, Lakowicz *et al.*, U.S. Patent No. 5,631,169; Stavrianopoulos, *et al.*, U.S. Patent No. 4,868,103). A fluorophore label on the first, 'donor' molecule is selected such that, upon excitation with incident light of appropriate wavelength, its emitted fluorescent energy will be absorbed by a fluorescent label on a second 'acceptor' molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter).

In another embodiment, determination of the ability of a probe to recognize a marker can be accomplished without labeling either assay component (probe or marker) by utilizing a technology such as real-time Biomolecular Interaction Analysis (BIA) (see, *e.g.*, Sjolander, S. and Urbaniczky, C., 1991, *Anal. Chem.* 63:2338-2345 and Szabo *et al.,* 1995, *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" or "surface plasmon resonance" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index of light near the surface (the optical phenomenon of surface plasmon resonance (SPR)), resulting in a detectable signal which can be used as an indication of real-time reactions between biological molecules.

Alternatively, in another embodiment, analogous diagnostic and prognostic assays can be conducted with marker and probe as solutes in a liquid phase. In such an assay, the complexed marker and probe are separated from uncomplexed components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, marker/probe complexes may be separated from uncomplexed assay components through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., 1993, *Trends Biochem Sci.* 18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the marker/probe complex as compared to the uncomplexed components may be exploited to differentiate the complex from uncomplexed components, for example through the utilization of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, *e.g.*, Heegaard, N.H., 1998, *J. Mol. Recognit.* Winter 11(1-6):141-8; Hage, D.S., and Tweed, S.A. *J Chromatogr B Biomed Sci Appl* 1997 Oct 10;699(1-2):499-525). Gel electrophoresis may also be employed to separate complexed assay components from unbound components (see, *e.g.*, Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, 1987-1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, non-denaturing gel matrix materials and conditions in the absence of reducing agent are typically preferred. Appropriate conditions to the particular assay and components thereof will be well known to one skilled in the art.

In a particular embodiment, the level of marker mRNA can be determined both by *in situ* and by *in vitro* formats in a biological sample using methods known in the art. The term "biological sample" is intended to include tissues, cells, biological fluids and isolates thereof, isolated from a subject, as well as tissues, cells and fluids present within a subject. Many expression detection methods use isolated RNA.

For *in vitro* methods, any RNA isolation technique that does not select against the isolation of mRNA can be utilized for the purification of RNA from cervical cells (see, *e.g.*, Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York 1987-1999). Additionally, large numbers of tissue samples can readily be processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski (1989, U.S. Patent No. 4,843,155).

The isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction analyses and probe arrays. One preferred diagnostic method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to a mRNA or genomic DNA encoding a marker of the present invention. Other suitable probes for use in the diagnostic assays of the invention are described herein. Hybridization of an mRNA with the probe indicates that the marker in question is being expressed.

In one format, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative format, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in detecting the level of mRNA encoded by the markers of the present invention.

An alternative method for determining the level of mRNA marker in a sample involves the process of nucleic acid amplification, *e.g.*, by rtPCR (the experimental embodiment set forth in Mullis, 1987, U.S. Patent No. 4,683,202), ligase chain reaction (Barany, 1991, *Proc. Natl. Acad. Sci. USA,* 88:189-193), self sustained sequence replication (Guatelli *et al.*, 1990, *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.*, 1988, *Bio/Technology* 6:1197), rolling circle replication (Lizardi *et al.*, U.S. Patent No. 5,854,033) or any other nucleic acid

amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. As used herein, amplification primers are defined as being a pair of nucleic acid molecules that can anneal to 5' or 3' regions of a gene (plus and minus strands, respectively, or vice-versa) and contain a short region in between. In general, amplification primers are from about 10 to 30 nucleotides in length and flank a region from about 50 to 200 nucleotides in length. Under appropriate conditions and with appropriate reagents, such primers permit the amplification of a nucleic acid molecule comprising the nucleotide sequence flanked by the primers.

For *in situ* methods, mRNA does not need to be isolated from the cervical cells prior to detection. In such methods, a cell or tissue sample is prepared/processed using known histological methods. The sample is then immobilized on a support, typically a glass slide, and then contacted with a probe that can hybridize to mRNA that encodes the marker.

As an alternative to making determinations based on the absolute expression level of the marker, determinations may be based on the normalized expression level of the marker. Expression levels are normalized by correcting the absolute expression level of a marker by comparing its expression to the expression of a gene that is not a marker, *e.g.*, a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene, or epithelial cell-specific genes. This normalization allows the comparison of the expression level in one sample, *e.g.*, a patient sample, to another sample, *e.g.*, a non-cervical cancer sample, or between samples from different sources.

Alternatively, the expression level can be provided as a relative expression level. To determine a relative expression level of a marker, the level of expression of the marker is determined for 10 or more samples of normal versus cancer cell isolates, preferably 50 or more samples, prior to the determination of the expression level for the sample in question. The mean expression level of each of the genes assayed in the larger number of samples is determined and this is used as a baseline expression level for the marker. The expression level of the marker determined for the test sample (absolute level of expression) is then divided by the mean expression value obtained for that marker. This provides a relative expression level.

Preferably, the samples used in the baseline determination will be from cervical cancer or from non-cervical cancer cells of cervical tissue. The choice of the cell source is dependent on the use of the relative expression level. Using expression found in normal tissues as a mean expression score aids in validating whether the marker assayed is cervical specific (versus normal cells). In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from cervical cells provides a means for grading the severity of the cervical cancer state.

In another embodiment of the present invention, a marker protein is detected. A preferred agent for detecting marker protein of the invention is an antibody capable of binding to such a protein or a fragment thereof, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment or derivative thereof (*e.g.*, Fab or $F(ab')_2$) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

Proteins from cervical cells can be isolated using techniques that are well known to those of skill in the art. The protein isolation methods employed can, for example, be such as those described in Harlow and Lane (Harlow and Lane, 1988, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York).

A variety of formats can be employed to determine whether a sample contains a protein that binds to a given antibody. Examples of such formats include, but are not limited to, enzyme immunoassay (EIA), radioimmunoassay (RIA), Western blot analysis and enzyme linked immunoabsorbant assay (ELISA). A skilled artisan can readily adapt known protein/antibody detection methods for use in determining whether cervical cells express a marker of the present invention.

In one format, antibodies, or antibody fragments or derivatives, can be used in methods such as Western blots or immunofluorescence techniques to detect the expressed proteins. In such uses, it is generally preferable to immobilize either the antibody or proteins on a solid support. Suitable solid phase supports or carriers include any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

One skilled in the art will know many other suitable carriers for binding antibody or antigen, and will be able to adapt such support for use with the present invention. For example, protein isolated from cervical cells can be run on a polyacrylamide gel electrophoresis and immobilized onto a solid phase support such as nitrocellulose. The support can then be washed with suitable buffers followed by treatment with the detectably labeled antibody. The solid phase support can then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on the solid support can then be detected by conventional means.

The invention also encompasses kits for detecting the presence of a marker protein or nucleic acid in a biological sample (*e.g.,* cervical smear). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing cervical cancer. For example, the kit can comprise a labeled compound or agent capable of detecting a marker protein or nucleic acid in a biological sample and means for determining the amount of the protein or mRNA in the sample (*e.g.*, an antibody which binds the protein or a fragment thereof, or an oligonucleotide probe which binds to DNA or mRNA encoding the protein). Kits can also include instructions for interpreting the results obtained using the kit.

For antibody-based kits, the kit can comprise, for example: (1) a first antibody (*e.g.*, attached to a solid support) which binds to a marker protein; and, optionally, (2) a second, different antibody which binds to either the protein or the first antibody and is conjugated to a detectable label.

For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, *e.g.*, a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a marker protein or (2) a pair of primers useful for amplifying a marker nucleic acid molecule. The kit can also comprise, *e.g.*, a buffering agent, a preservative, or a protein stabilizing agent. The kit can further comprise components

necessary for detecting the detectable label (*e.g.*, an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit.

B. Pharmacogenomics

The markers of the invention are also useful as pharmacogenomic markers. As used herein, a "pharmacogenomic marker" is an objective biochemical marker whose expression level correlates with a specific clinical drug response or susceptibility in a patient (see, *e.g.*, McLeod *et al.* (1999) *Eur. J. Cancer* 35(12): 1650-1652). The presence or quantity of the pharmacogenomic marker expression is related to the predicted response of the patient and more particularly the patient's tumor to therapy with a specific drug or class of drugs. By assessing the presence or quantity of the expression of one or more pharmacogenomic markers in a patient, a drug therapy which is most appropriate for the patient, or which is predicted to have a greater degree of success, may be selected. For example, based on the presence or quantity of RNA or protein encoded by specific tumor markers in a patient, a drug or course of treatment may be selected that is optimized for the treatment of the specific tumor likely to be present in the patient. The use of pharmacogenomic markers therefore permits selecting or designing the most appropriate treatment for each cancer patient without trying different drugs or regimes.

Another aspect of pharmacogenomics deals with genetic conditions that alters the way the body acts on drugs. These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show

exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, a PM will show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the level of expression of a marker of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a modulator of expression of a marker of the invention.

C. Monitoring Clinical Trials

Monitoring the influence of agents (*e.g.*, drug compounds) on the level of expression of a marker of the invention can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent to affect marker expression can be monitored in clinical trials of subjects receiving treatment for cervical cancer. In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of one or more selected markers of the invention in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the

level of expression of the marker(s) in the post-administration samples; (v) comparing the level of expression of the marker(s) in the pre-administration sample with the level of expression of the marker(s) in the post-administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased expression of the marker gene(s) during the course of treatment may indicate ineffective dosage and the desirability of increasing the dosage. Conversely, decreased expression of the marker gene(s) may indicate efficacious treatment and no need to change dosage.

D. Electronic Apparatus Readable Media and Arrays

Electronic apparatus readable media comprising a marker of the present invention is also provided. As used herein, "electronic apparatus readable media" refers to any suitable medium for storing, holding or containing data or information that can be read and accessed directly by an electronic apparatus. Such media can include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as compact disc; electronic storage media such as RAM, ROM, EPROM, EEPROM and the like; general hard disks and hybrids of these categories such as magnetic/optical storage media. The medium is adapted or configured for having recorded thereon a marker of the present invention.

As used herein, the term "electronic apparatus" is intended to include any suitable computing or processing apparatus or other device configured or adapted for storing data or information. Examples of electronic apparatus suitable for use with the present invention include stand-alone computing apparatus; networks, including a local area network (LAN), a wide area network (WAN) Internet, Intranet, and Extranet; electronic appliances such as a personal digital assistants (PDAs), cellular phone, pager and the like; and local and distributed processing systems.

As used herein, "recorded" refers to a process for storing or encoding information on the electronic apparatus readable medium. Those skilled in the art can readily adopt any of the presently known methods for recording information on known media to generate manufactures comprising the markers of the present invention.

A variety of software programs and formats can be used to store the marker information of the present invention on the electronic apparatus readable medium. For example, the marker nucleic acid sequence can be represented in a word

processing text file, formatted in commercially-available software such as WordPerfect and MicroSoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like, as well as in other forms. Any number of data processor structuring formats (*e.g.*, text file or database) may be employed in order to obtain or create a medium having recorded thereon the markers of the present invention.

By providing the markers of the invention in readable form, one can routinely access the marker sequence information for a variety of purposes. For example, one skilled in the art can use the nucleotide or amino acid sequences of the present invention in readable form to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of the sequences of the invention which match a particular target sequence or target motif.

The present invention therefore provides a medium for holding instructions for performing a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer, wherein the method comprises the steps of determining the presence or absence of a marker and based on the presence or absence of the marker, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer and/or recommending a particular treatment for cervical cancer or pre-cervical cancer condition.

The present invention further provides in an electronic system and/or in a network, a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer associated with a marker wherein the method comprises the steps of determining the presence or absence of the marker, and based on the presence or absence of the marker, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer, and/or recommending a particular treatment for the cervical cancer or pre-cervical cancer condition. The method may further comprise the step of receiving phenotypic information associated with the subject and/or acquiring from a network phenotypic information associated with the subject.

The present invention also provides in a network, a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer associated with a marker, said method comprising the steps of receiving information associated with the marker receiving phenotypic information associated with the subject,

acquiring information from the network corresponding to the marker and/or cervical cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has a cervical cancer or a pre-disposition to cervical cancer. The method may further comprise the step of recommending a particular treatment for the cervical cancer or pre-cervical cancer condition.

The present invention also provides a business method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer, said method comprising the steps of receiving information associated with the marker, receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or cervical cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer. The method may further comprise the step of recommending a particular treatment for the cervical cancer or pre-cervical cancer condition.

The invention also includes an array comprising a marker of the present invention. The array can be used to assay expression of one or more genes in the array. In one embodiment, the array can be used to assay gene expression in a tissue to ascertain tissue specificity of genes in the array. In this manner, up to about 7600 genes can be simultaneously assayed for expression. This allows a profile to be developed showing a battery of genes specifically expressed in one or more tissues.

In addition to such qualitative determination, the invention allows the quantitation of gene expression. Thus, not only tissue specificity, but also the level of expression of a battery of genes in the tissue is ascertainable. Thus, genes can be grouped on the basis of their tissue expression *per se* and level of expression in that tissue. This is useful, for example, in ascertaining the relationship of gene expression between or among tissues. Thus, one tissue can be perturbed and the effect on gene expression in a second tissue can be determined. In this context, the effect of one cell type on another cell type in response to a biological stimulus can be determined. Such a determination is useful, for example, to know the effect of cell-cell interaction at the level of gene expression. If an agent is administered therapeutically to treat one cell type but has an undesirable effect on another cell type, the invention provides an assay to determine the molecular basis of the undesirable effect and thus provides the

opportunity to co-administer a counteracting agent or otherwise treat the undesired effect. Similarly, even within a single cell type, undesirable biological effects can be determined at the molecular level. Thus, the effects of an agent on expression of other than the target gene can be ascertained and counteracted.

In another embodiment, the array can be used to monitor the time course of expression of one or more genes in the array. This can occur in various biological contexts, as disclosed herein, for example development of cervical cancer, progression of cervical cancer, and processes, such a cellular transformation associated with cervical cancer.

The array is also useful for ascertaining the effect of the expression of a gene on the expression of other genes in the same cell or in different cells. This provides, for example, for a selection of alternate molecular targets for therapeutic intervention if the ultimate or downstream target cannot be regulated.

The array is also useful for ascertaining differential expression patterns of one or more genes in normal and abnormal cells. This provides a battery of genes that could serve as a molecular target for diagnosis or therapeutic intervention.

E. Surrogate Markers

The markers of the invention may serve as surrogate markers for one or more disorders or disease states or for conditions leading up to disease states, and in particular, cervical cancer. As used herein, a "surrogate marker" is an objective biochemical marker which correlates with the absence or presence of a disease or disorder, or with the progression of a disease or disorder (*e.g.*, with the presence or absence of a tumor). The presence or quantity of such markers is independent of the disease. Therefore, these markers may serve to indicate whether a particular course of treatment is effective in lessening a disease state or disorder. Surrogate markers are of particular use when the presence or extent of a disease state or disorder is difficult to assess through standard methodologies (*e.g.*, early stage tumors), or when an assessment of disease progression is desired before a potentially dangerous clinical endpoint is reached (*e.g.*, an assessment of cardiovascular disease may be made using cholesterol levels as a surrogate marker, and an analysis of HIV infection may be made using HIV RNA levels as a surrogate marker, well in advance of the undesirable clinical outcomes of myocardial infarction or fully-developed AIDS). Examples of the use of surrogate

markers in the art include: Koomen *et al.* (2000) *J. Mass. Spectrom.* 35: 258-264; and James (1994) *AIDS Treatment News Archive* 209.

The markers of the invention are also useful as pharmacodynamic markers. As used herein, a "pharmacodynamic marker" is an objective biochemical marker which correlates specifically with drug effects. The presence or quantity of a pharmacodynamic marker is not related to the disease state or disorder for which the drug is being administered; therefore, the presence or quantity of the marker is indicative of the presence or activity of the drug in a subject. For example, a pharmacodynamic marker may be indicative of the concentration of the drug in a biological tissue, in that the marker is either expressed or transcribed or not expressed or transcribed in that tissue in relationship to the level of the drug. In this fashion, the distribution or uptake of the drug may be monitored by the pharmacodynamic marker. Similarly, the presence or quantity of the pharmacodynamic marker may be related to the presence or quantity of the metabolic product of a drug, such that the presence or quantity of the marker is indicative of the relative breakdown rate of the drug *in vivo*. Pharmacodynamic markers are of particular use in increasing the sensitivity of detection of drug effects, particularly when the drug is administered in low doses. Since even a small amount of a drug may be sufficient to activate multiple rounds of marker transcription or expression, the amplified marker may be in a quantity which is more readily detectable than the drug itself. Also, the marker may be more easily detected due to the nature of the marker itself; for example, using the methods described herein, antibodies may be employed in an immune-based detection system for a protein marker, or marker-specific radiolabeled probes may be used to detect a mRNA marker. Furthermore, the use of a pharmacodynamic marker may offer mechanism-based prediction of risk due to drug treatment beyond the range of possible direct observations. Examples of the use of pharmacodynamic markers in the art include: Matsuda *et al.* US 6,033,862; Hattis *et al.* (1991) *Env. Health Perspect.* 90: 229-238; Schentag (1999) *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S21-S24; and Nicolau (1999) *Am, J. Health-Syst. Pharm.* 56 Suppl. 3: S16-S20.

VI. Experimental Protocol

A. Identification of clones

Cervical tumor specific cDNA clones were identified by transcription profiling using mRNA from 12 cervical tumors, 5 CIN III, 5 CIN I and 12 normal cervical tissues. The subtracted libraries were constructed using mRNA from at least three independent normal ectocervix, B-lymphocytes, T-lymphocytes and other white blood cells (in activated and resting states) as drivers and four independent stage 1B cervical tumors or four independent C1N III cervical samples as testers. The top up-regulated clones in tumors or C1N III cervical tissues, as determined by proprietary statistical analysis methods, were selected. The clusters in which the selected clones belong were blasted against both public and proprietary sequence databases in order to identify other EST sequences or clusters with significant overlap. Thus, contiguous EST sequences and/or clusters were assembled into full-length genes.

An identification of protein sequence corresponding to the clone was accomplished by obtaining one of the following:

a) a direct match between the protein sequence and at least one EST sequence in one of its 6 possible translations;

b) a direct match between the nucleotide sequence for the mRNA corresponding to the protein sequence and at least one EST sequence;

c) a match between the protein sequence and a contiguous assembly (contig) of the EST sequences with other available EST sequences in the databases in one of its 6 possible translations; or

d) a match between the nucleotide sequence for the mRNA corresponding to the protein sequence and a contiguous assembly of the EST sequences with other available EST sequences in the databases in one of its 6 possible translations.

VII. Summary of the Data

Tables 1-3 list the markers obtained using the foregoing protocol. The tables provide the name of the gene corresponding to the marker ("Gene Name"), the sequence listing identifier of the cDNA sequence of a nucleotide transcript encoded by or corresponding to the marker ("SEQ ID NO (nts)"), the sequence listing identifier of the amino acid sequence of a protein encoded by the nucleotide transcript ("SEQ ID NO

(AAs)"), and the location of the protein coding sequence within the cDNA sequence ("CDS").

Table 1 lists all of the markers of the invention which are over-expressed in cervical cancer cells compared to normal (*i.e.,* non-cancerous) cervical cells. Table 2 lists newly-identified nucleotide and amino acid sequences useful as cervical cancer markers. Table 3 lists newly-identified nucleotide sequences useful as cervical cancer markers.

Other Embodiments

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims:

What is claimed:

1. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 143, 145, 147, 149, 151, 167, 203, 217, 231, 233, 51, 65, 67, 68, 100, and 153.

2. A vector which contains the nucleic acid molecule of claim 1.

3. A host cell which contains the nucleic acid molecule of claim 1.

4. A method of assessing whether a patient is afflicted with cervical cancer, the method comprising comparing:

a) the level of expression of a marker in a patient sample, wherein the marker is selected from Table 1; and

b) the normal level of expression of the marker in a control non-cervical cancer sample,

wherein a significant increase in the level of expression of the marker in the patient sample and the normal level is an indication that the patient is afflicted with cervical cancer.

5. An isolated polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 143, 145, 147, 149, 151, 167, 203, 217, 231, and 233.

6. An antibody which selectively binds to the polypeptide of claim 5.

7. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 144, 146, 148, 150, 152, 168, 204, 218, 232, and 234.

8. An antibody which selectively binds to the polypeptide of claim 7.

SEQUENCE LISTING

<110> Millennium Pharmaceuticals, Inc. et al.

<120> NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF CERVICAL CANCER

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Val Ser Ala His His Asp Leu Asn Ile Asp Gln Ser Gln Cys Asn Glu
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Met Tyr Ile Asn Ser Ser Gln Arg Val Glu Ser Thr Val Ile Pro Glu
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Ser Thr Ile Met Arg Thr Leu His Ser Gly Glu Ile Thr Ser His Glu
                85                  90                  95
Gln Gly Phe Ser Val Glu Leu Glu Ser Glu Ile Ser Thr Thr Ala Asp
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Asp Cys Ser Ser Glu Val Asn Gly Cys Ser Phe Val Met Arg Thr Gly
        115                 120                 125
Lys Pro Thr Asn Leu Leu Arg Glu Glu Glu Phe Gly Val Asp Asp Ser
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Val Trp Glu Lys Glu Ile Glu Ile Leu Ile Glu Glu Asn Glu Asp Leu
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Val Ser Ala His His Asp Leu Asn Ile Asp Gln Ser Gln Cys Asn Glu
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Met Tyr Ile Asn Ser Ser Gln Arg Val Glu Ser Thr Val Ile Pro Glu
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Ser Thr Ile Met Arg Thr Leu His Ser Gly Glu Ile Thr Ser His Glu
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Gln Gly Phe Ser Val Glu Leu Glu Ser Glu Ile Ser Thr Thr Ala Asp
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Asp Cys Ser Ser Glu Val Asn Gly Cys Ser Phe Val Met Arg Thr Gly
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Lys Pro Thr Asn Leu Leu Arg Glu Glu Glu Phe Gly Val Asp Asp Ser
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Tyr Ser Glu Gln Gly Ala Gln Asp Ser Pro Thr His Leu Glu Met Met
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Glu Ser Glu Leu Ala Gly Lys Gln His Glu Ile Glu Glu Leu Asn Arg
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Glu Leu Glu Glu Met Arg Val Thr Tyr Gly Thr Glu Gly Leu Gln Gln
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Leu Gln Glu Phe Glu Ala Ala Ile Lys Gln Arg Asp Gly Ile Ile Thr
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Gln Leu Thr Ala Asn Leu Gln Gln Ala Arg Arg Glu Lys Asp Glu Thr
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Met Arg Glu Phe Leu Glu Leu Thr Glu Gln Ser Gln Lys Leu Gln Ile
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Gln Phe Gln Gln Leu Gln Ala Ser Glu Thr Leu Arg Asn Ser Thr His
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Ser Ser Thr Ala Ala Asp Leu Leu Gln Ala Lys Gln Gln Ile Leu Thr
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His Gln Gln Gln Leu Glu Glu Gln Asp His Leu Leu Glu Asp Tyr Gln
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Lys Lys Lys Glu Asp Phe Thr Met Gln Ile Ser Phe Leu Gln Glu Lys
290 295 300
Ile Lys Val Tyr Glu Met Glu Gln Asp Lys Lys Val Glu Asn Ser Asn
305 310 315 320
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Gln Lys Glu Arg Gln Ser Ser Glu Glu Ile Lys Gln Leu Met Gly Thr
385                 390                 395                 400
Val Glu Glu Leu Gln Lys Arg Asn His Lys Asp Ser Gln Phe Glu Thr
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Asp Ile Val Gln Arg Met Glu Gln Glu Thr Gln Arg Lys Leu Glu Gln
            420                 425                 430
Leu Arg Ala Glu Leu Asp Glu Met Tyr Gly Gln Gln Ile Val Gln Met
        435                 440                 445
Lys Gln Glu Leu Ile Arg Gln His Met Ala Gln Met Glu Glu Met Lys
    450                 455                 460
Thr Arg His Lys Gly Glu Met Glu Asn Ala Leu Arg Ser Tyr Ser Asn
465                 470                 475                 480
Ile Thr Val Asn Glu Asp Gln Ile Lys Leu Met Asn Val Ala Ile Asn
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Glu Leu Asn Ile Lys Leu Gln Asp Thr Asn Ser Gln Lys Glu Lys Leu
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Lys Glu Glu Leu Gly Leu Ile Leu Glu Glu Lys Cys Ala Leu Gln Arg
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Gln Leu Glu Asp Leu Val Glu Glu Leu Ser Phe Ser Arg Glu Gln Ile
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Gln Arg Ala Arg Gln Thr Ile Ala Glu Gln Glu Ser Lys Leu Asn Glu
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Val Thr Asn Tyr Lys Ile Lys Leu Glu Met Leu Glu Lys Glu Lys Asn
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Lys Glu Asp Leu Glu Ile Glu His Arg Ile Asn Ile Glu Lys Leu Lys
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Asp Asn Leu Gly Ile His Tyr Lys Gln Gln Ile Asp Gly Leu Gln Asn
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Glu Met Ser Gln Lys Ile Glu Thr Met Gln Phe Glu Lys Asp Asn Leu
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Ile Thr Lys Gln Asn Gln Leu Ile Leu Glu Ile Ser Lys Leu Lys Asp
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Leu Gln Gln Ser Leu Val Asn Ser Lys Ser Glu Glu Met Thr Leu Gln
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Glu Lys Gly Thr Leu Glu Gln Glu Val Gln Glu Leu Gln Leu Lys Thr
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Glu Leu Leu Glu Lys Gln Met Lys Glu Lys Glu Asn Asp Leu Gln Glu
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Lys Phe Ala Gln Leu Glu Ala Glu Asn Ser Ile Leu Lys Asp Glu Lys
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Lys Thr Leu Glu Asp Met Leu Lys Ile His Thr Pro Val Ser Gln Glu
785                 790                 795                 800
Glu Arg Leu Ile Phe Leu Asp Ser Ile Lys Ser Lys Ser Lys Asp Ser
                805                 810                 815
Val Trp Glu Lys Glu Ile Glu Ile Leu Ile Glu Glu Asn Glu Asp Leu
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Lys Gln Gln Cys Ile Gln Leu Asn Glu Glu Ile Glu Lys Gln Arg Asn
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Gln Glu Glu Tyr Ala Cys Leu Leu Lys Val Lys Asp Asp Leu Glu Asp
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Ser Lys Asn Lys Gln Glu Leu Glu Tyr Lys Ser Lys Leu Lys Ala Leu
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Asn Glu Glu Leu His Leu Gln Arg Ile Asn Pro Thr Thr Val Lys Met
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Lys Ser Ser Val Phe Asp Glu Asp Lys Thr Phe Val Ala Glu Thr Leu
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Glu Met Gly Glu Val Val Glu Lys Asp Thr Thr Glu Leu Met Glu Lys
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Arg Cys Arg Glu Leu Glu Ile Ile Ile Asn His Asn Arg Ala Glu Asn
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Pro Ser Glu Asn Asp Lys Leu Gln Lys Glu Leu Asn Val Leu Lys Ser
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Ser Leu Val Tyr Ser Thr His Val Asp Gln Val Arg Glu Tyr Met Glu
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Ala Gln Glu Glu Lys Ile Lys Glu Leu Gln Lys Ile His Gln Leu Glu
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Leu Gln Thr Met Lys Thr Gln Glu Thr Gly Asp Glu Gly Lys Pro Leu
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His Leu Leu Ile Gly Lys Leu Gln Lys Ala Val Ser Glu Glu Cys Ser
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Tyr Phe Leu Gln Thr Leu Cys Ser Val Leu Gly Glu Tyr Tyr Thr Pro
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Ala Leu Lys Cys Glu Val Asn Ala Glu Asp Lys Glu Asn Ser Gly Asp
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Tyr Ile Ser Glu Asn Glu Asp Pro Glu Leu Gln Asp Tyr Arg Tyr Glu
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Val Gln Asp Phe Gln Glu Asn Met His Thr Leu Leu Asn Lys Val Thr
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Glu Glu Tyr Asn Lys Leu Leu Val Leu Gln Thr Arg Leu Ser Lys Ile
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Trp Gly Gln Gln Thr Asp Gly Met Lys Leu Glu Phe Gly Glu Glu Asn
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Leu Pro Lys Glu Glu Thr Glu Phe Leu Ser Ile His Ser Gln Met Thr
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Glu Ser Thr Val Pro Pro Ser Leu Pro Val Asp Ser Val Val Ile Thr
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Glu Ser Asp Ala Gln Arg Thr Met Tyr Pro Gly Ser Cys Val Lys Lys
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Gln Gln Thr Glu Leu Ser Arg Ile Ser Gly Gly Lys Glu Asn Thr Ala
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Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe
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Phe Ser Lys Asp Lys Thr Phe Ile Val Arg Gln Ser Ile His Asp Glu
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His Gln Gln Ala Thr Glu Leu Leu Arg Gln Ala His Met Arg Gln Met
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Gln Ile Gln Glu Lys Thr Asp Ile Ile Asp Arg Leu Glu Gln Glu Leu
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Ala Glu Ala Gly Pro Val Glu Gln Gln Leu Leu Gln Glu Thr Glu Lys
1985                1990                1995                2000
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Val Pro Arg Phe Gln Pro Ile Ser Glu His Gln Thr Arg Glu Val Glu
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2675 2680 2685
Glu Ser Val Ala Thr Lys Ala Glu Leu Ala Ser Tyr Lys Glu Lys Ala
2690 2695 2700
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Ser Ile Ala Ser Gln Thr Asp Gly Thr Leu Lys Ile Ser Ser Ser Asn
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Gln Thr Pro Gln Ile Leu Val Lys Asn Ala Gly Ile Gln Ile Asn Leu
2785                2790                2795                2800
Gln Ser Glu Cys Ser Ser Glu Glu Val Thr Glu Ile Ile Ser Gln Phe
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Thr Glu Lys Ile Glu Lys Met Gln Glu Leu His Ala Ala Glu Ile Leu
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Asp Met Glu Ser Arg His Ile Ser Glu Thr Glu Thr Leu Lys Arg Glu
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His Tyr Val Ala Val Gln Leu Leu Lys Glu Glu Cys Gly Thr Leu Lys
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Ala Val Ile Gln Cys Leu Arg Ser Lys Glu Gly Ser Ser Ile Pro Glu
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<212> PRT
<213> Homo sapiens

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            20   25   30
Ser Lys Lys Gln Lys Lys Lys Arg Lys Thr Ser Ser Ser Lys His Asp
        35   40   45
Val Ser Ala His His Asp Leu Asn Ile Asp Gln Ser Gln Cys Asn Glu
    50   55   60
Met Tyr Ile Asn Ser Ser Gln Arg Val Glu Ser Thr Val Ile Pro Glu
65   70   75   80
Ser Thr Ile Met Arg Thr Leu His Ser Gly Glu Ile Thr Ser His Glu
                85   90   95
Gln Gly Phe Ser Val Glu Leu Glu Ser Glu Ile Ser Thr Thr Ala Asp
            100   105   110
Asp Cys Ser Ser Glu Val Asn Gly Cys Ser Phe Val Met Arg Thr Gly
        115   120   125
Lys Pro Thr Asn Leu Leu Arg Glu Glu Glu Phe Gly Val Asp Asp Ser
    130   135   140
Tyr Ser Glu Gln Gly Ala Gln Asp Ser Pro Thr His Leu Glu Met Met
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Glu Ser Glu Leu Ala Gly Lys Gln His Glu Ile Glu Glu Leu Asn Arg
                165   170   175
Glu Leu Glu Glu Met Arg Val Thr Tyr Gly Thr Glu Gly Leu Gln Gln
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Leu Gln Glu Phe Glu Ala Ala Ile Lys Gln Arg Asp Gly Ile Ile Thr
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Gln Leu Thr Ala Asn Leu Gln Gln Ala Arg Arg Glu Lys Asp Glu Thr
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Met Arg Glu Phe Leu Glu Leu Thr Glu Gln Ser Gln Lys Leu Gln Ile
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Gln Phe Gln Gln Leu Gln Ala Ser Glu Thr Leu Arg Asn Ser Thr His
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Ser Ser Thr Ala Ala Asp Leu Leu Gln Ala Lys Gln Gln Ile Leu Thr
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His Gln Gln Gln Leu Glu Glu Gln Asp His Leu Leu Glu Asp Tyr Gln
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Lys Lys Lys Glu Asp Phe Thr Met Gln Ile Ser Phe Leu Gln Glu Lys
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Thr Arg His Lys Gly Glu Met Glu Asn Ala Leu Arg Ser Tyr Ser Asn
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Lys Glu Asp Leu Glu Ile Glu His Arg Ile Asn Ile Glu Lys Leu Lys
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Asp Asn Leu Gly Ile His Tyr Lys Gln Gln Ile Asp Gly Leu Gln Asn
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Glu Lys Gly Thr Leu Glu Gln Glu Val Gln Glu Leu Gln Leu Lys Thr
740 745 750
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755 760 765
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Val Trp Glu Lys Glu Ile Glu Ile Leu Ile Glu Glu Asn Glu Asp Leu
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835 840 845
Thr Phe Ser Phe Ala Glu Lys Asn Phe Glu Val Asn Tyr Gln Glu Leu
850 855 860
Gln Glu Glu Tyr Ala Cys Leu Leu Lys Val Lys Asp Asp Leu Glu Asp
865 870 875 880
Ser Lys Asn Lys Gln Glu Leu Glu Tyr Lys Ser Lys Leu Lys Ala Leu
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Lys Ser Ser Val Phe Asp Glu Asp Lys Thr Phe Val Ala Glu Thr Leu
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Glu Met Gly Glu Val Val Glu Lys Asp Thr Thr Glu Leu Met Glu Lys
930 935 940
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1825 1830 1835 1840
Glu Leu Met Leu Asn Ile Ser Ser Arg Leu Gln Ala Ala Val Glu Lys
1845 1850 1855
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1860 1865 1870
Val Thr Gln Thr Glu Leu Met Arg Glu Ser Phe Arg Gln Lys Gln Glu
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Ala Thr Glu Ser Leu Lys Cys Gln Glu Glu Leu Arg Glu Arg Leu His
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Gln Ile Gln Glu Lys Thr Asp Ile Ile Asp Arg Leu Glu Gln Glu Leu
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1955 1960 1965
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1970 1975 1980
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    2530   2535   2540
Lys Ile Val Glu Glu Lys Val Ala Ala Ala Leu Val Ser Gln Ile Gln
2545   2550   2555   2560
Leu Glu Ala Val Gln Glu Tyr Ala Lys Phe Cys Gln Asp Asn Gln Thr
                2565   2570   2575
Ile Ser Ser Glu Pro Glu Arg Thr Asn Ile Gln Asn Leu Asn Gln Leu
            2580   2585   2590
Arg Glu Asp Glu Leu Gly Ser Asp Ile Ser Ala Leu Thr Leu Arg Ile
        2595   2600   2605
Ser Glu Leu Glu Ser Gln Val Val Glu Met His Thr Ser Leu Ile Leu
    2610   2615   2620
Glu Lys Glu Gln Val Glu Ile Ala Glu Lys Asn Val Leu Glu Lys Glu
2625   2630   2635   2640
Lys Lys Leu Leu Glu Leu Gln Lys Leu Leu Glu Gly Asn Glu Lys Lys
                2645   2650   2655
Gln Arg Glu Lys Glu Lys Lys Arg Ser Pro Gln Asp Val Glu Val Leu
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Lys Thr Thr Thr Glu Leu Phe His Ser Asn Glu Glu Ser Gly Phe Phe

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Val Thr Glu Ile Ile Ser Gln Phe Thr Glu Lys Ile Glu Lys Met Gln
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Val Glu Tyr Gln Ala Ala Met Glu Cys Leu Gln Lys Ala Asp Arg Arg
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Ser Leu Leu Ser Glu Ile Gln Ala Leu His Ala Gln Met Asn Gly Arg
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Lys Ile Thr Leu Lys Arg Glu Gln Glu Ser Glu Lys Pro Ser Gln Glu
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Leu Leu Glu Tyr Asn Ile Gln Gln Lys Gln Ser Gln Met Leu Glu Met
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Gln Val Glu Leu Ser Ser Met Lys Asp Arg Ala Thr Glu Leu Gln Glu
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Asp Glu Val His Leu Leu Asn Asp Thr Leu Ala Ser Glu Gln Lys Lys
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Ser Arg Glu Leu Gln Trp Ala Leu Glu Lys Glu Lys Ala Lys Leu Gly
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Arg Ser Glu Glu Arg Asp Lys Glu Glu Leu Glu Asp Leu Lys Phe Ser
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Ser Ser Thr Leu Asp Arg Glu Arg Glu Leu His Ala Gln Leu Gln Ser
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Ser Asp Gly Thr Gly Gln Ser Arg Pro Pro Leu Pro Ser Glu Asp Leu
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<212> PRT
<213> Homo sapiens

<400> 8

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Leu Ala Gln Phe Arg Gln Arg Lys Ala Gln Ser Asp Gly Gln Ser Pro
            20                  25                  30
Ser Lys Lys Gln Lys Lys Lys Arg Lys Thr Ser Ser Ser Lys His Asp
        35                  40                  45
Val Ser Ala His His Asp Leu Asn Ile Asp Gln Ser Gln Cys Asn Glu
    50                  55                  60
Met Tyr Ile Asn Ser Ser Gln Arg Val Glu Ser Thr Val Ile Pro Glu
65                  70                  75                  80
Ser Thr Ile Met Arg Thr Leu His Ser Gly Glu Ile Thr Ser His Glu
                85                  90                  95
Gln Gly Phe Ser Val Glu Leu Glu Ser Glu Ile Ser Thr Thr Ala Asp
            100                 105                 110
Asp Cys Ser Ser Glu Val Asn Gly Cys Ser Phe Val Met Arg Thr Gly
        115                 120                 125
Lys Pro Thr Asn Leu Leu Arg Glu Glu Glu Phe Gly Val Asp Asp Ser
    130                 135                 140
Tyr Ser Glu Gln Gly Ala Gln Asp Ser Pro Thr His Leu Glu Met Met
145                 150                 155                 160
Glu Ser Glu Leu Ala Gly Lys Gln His Glu Ile Glu Glu Leu Asn Arg
                165                 170                 175
Glu Leu Glu Glu Met Arg Val Thr Tyr Gly Thr Glu Gly Leu Gln Gln
            180                 185                 190
Leu Gln Glu Phe Glu Ala Ala Ile Lys Gln Arg Asp Gly Ile Ile Thr
        195                 200                 205
Gln Leu Thr Ala Asn Leu Gln Gln Ala Arg Arg Glu Lys Asp Glu Thr
    210                 215                 220
Met Arg Glu Phe Leu Glu Leu Thr Glu Gln Ser Gln Lys Leu Gln Ile
225                 230                 235                 240
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Gln Phe Gln Gln Leu Gln Ala Ser Glu Thr Leu Arg Asn Ser Thr His
                245                 250                 255
Ser Ser Thr Ala Ala Asp Leu Leu Gln Ala Lys Gln Gln Ile Leu Thr
            260                 265                 270
His Gln Gln Gln Leu Glu Glu Gln Asp His Leu Leu Glu Asp Tyr Gln
        275                 280                 285
Lys Lys Lys Glu Asp Phe Thr Met Gln Ile Ser Phe Leu Gln Glu Lys
    290                 295                 300
Ile Lys Val Tyr Glu Met Glu Gln Asp Lys Lys Val Glu Asn Ser Asn
305                 310                 315                 320
Lys Glu Glu Ile Gln Glu Lys Glu Thr Ile Ile Glu Glu Leu Asn Thr
                325                 330                 335
Lys Ile Ile Glu Glu Glu Lys Lys Thr Leu Glu Leu Lys Asp Lys Leu
            340                 345                 350
Thr Thr Ala Asp Lys Leu Leu Gly Glu Leu Gln Glu Gln Ile Val Gln
        355                 360                 365
Lys Asn Gln Glu Ile Lys Asn Met Lys Leu Glu Leu Thr Asn Ser Lys
    370                 375                 380
Gln Lys Glu Arg Gln Ser Ser Glu Glu Ile Lys Gln Leu Met Gly Thr
385                 390                 395                 400
Val Glu Glu Leu Gln Lys Arg Asn His Lys Asp Ser Gln Phe Glu Thr
                405                 410                 415
Asp Ile Val Gln Arg Met Glu Gln Glu Thr Gln Arg Lys Leu Glu Gln
            420                 425                 430
Leu Arg Ala Glu Leu Asp Glu Met Tyr Gly Gln Gln Ile Val Gln Met
        435                 440                 445
Lys Gln Glu Leu Ile Arg Gln His Met Ala Gln Met Glu Glu Met Lys
    450                 455                 460
Thr Arg His Lys Gly Glu Met Glu Asn Ala Leu Arg Ser Tyr Ser Asn
465                 470                 475                 480
Ile Thr Val Asn Glu Asp Gln Ile Lys Leu Met Asn Val Ala Ile Asn
                485                 490                 495
Glu Leu Asn Ile Lys Leu Gln Asp Thr Asn Ser Gln Lys Glu Lys Leu
            500                 505                 510
Lys Glu Glu Leu Gly Leu Ile Leu Glu Glu Lys Cys Ala Leu Gln Arg
        515                 520                 525
Gln Leu Glu Asp Leu Val Glu Glu Leu Ser Phe Ser Arg Glu Gln Ile
    530                 535                 540
Gln Arg Ala Arg Gln Thr Ile Ala Glu Gln Glu Ser Lys Leu Asn Glu
545                 550                 555                 560
Ala His Lys Ser Leu Ser Thr Val Glu Asp Leu Lys Ala Glu Ile Val
                565                 570                 575
Ser Ala Ser Glu Ser Arg Lys Glu Leu Glu Leu Lys His Glu Ala Glu
            580                 585                 590
Val Thr Asn Tyr Lys Ile Lys Leu Glu Met Leu Glu Lys Glu Lys Asn
        595                 600                 605
Ala Val Leu Asp Arg Met Ala Glu Ser Gln Glu Ala Glu Leu Glu Arg
    610                 615                 620
Leu Arg Thr Gln Leu Leu Phe Ser His Glu Glu Glu Leu Ser Lys Leu
625                 630                 635                 640
Lys Glu Asp Leu Glu Ile Glu His Arg Ile Asn Ile Glu Lys Leu Lys
                645                 650                 655
Asp Asn Leu Gly Ile His Tyr Lys Gln Gln Ile Asp Gly Leu Gln Asn
            660                 665                 670
Glu Met Ser Gln Lys Ile Glu Thr Met Gln Phe Glu Lys Asp Asn Leu
        675                 680                 685
Ile Thr Lys Gln Asn Gln Leu Ile Leu Glu Ile Ser Lys Leu Lys Asp
    690                 695                 700
Leu Gln Gln Ser Leu Val Asn Ser Lys Ser Glu Glu Met Thr Leu Gln
```

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705                 710                 715                 720
Ile Asn Glu Leu Gln Lys Glu Ile Glu Ile Leu Arg Gln Glu Glu Lys
                725                 730                 735
Glu Lys Gly Thr Leu Glu Gln Glu Val Gln Glu Leu Gln Leu Lys Thr
            740                 745                 750
Glu Leu Leu Glu Lys Gln Met Lys Glu Lys Glu Asn Asp Leu Gln Glu
        755                 760                 765
Lys Phe Ala Gln Leu Glu Ala Glu Asn Ser Ile Leu Lys Asp Glu Lys
    770                 775                 780
Lys Thr Leu Glu Asp Met Leu Lys Ile His Thr Pro Val Ser Gln Glu
785                 790                 795                 800
Glu Arg Leu Ile Phe Leu Asp Ser Ile Lys Ser Lys Ser Lys Asp Ser
                805                 810                 815
Val Trp Glu Lys Glu Ile Glu Ile Leu Ile Glu Glu Asn Glu Asp Leu
            820                 825                 830
Lys Gln Gln Cys Ile Gln Leu Asn Glu Glu Ile Glu Lys Gln Arg Asn
        835                 840                 845
Thr Phe Ser Phe Ala Glu Lys Asn Phe Glu Val Asn Tyr Gln Glu Leu
    850                 855                 860
Gln Glu Glu Tyr Ala Cys Leu Leu Lys Val Lys Asp Asp Leu Glu Asp
865                 870                 875                 880
Ser Lys Asn Lys Gln Glu Leu Glu Tyr Lys Ser Lys Leu Lys Ala Leu
                885                 890                 895
Asn Glu Glu Leu His Leu Gln Arg Ile Asn Pro Thr Thr Val Lys Met
            900                 905                 910
Lys Ser Ser Val Phe Asp Glu Asp Lys Thr Phe Val Ala Glu Thr Leu
        915                 920                 925
Glu Met Gly Glu Val Val Glu Lys Asp Thr Thr Glu Leu Met Glu Lys
    930                 935                 940
Leu Glu Val Thr Lys Arg Glu Lys Leu Glu Leu Ser Gln Arg Leu Ser
945                 950                 955                 960
Asp Leu Ser Glu Gln Leu Lys Gln Lys His Gly Glu Ile Ser Phe Leu
                965                 970                 975
Asn Glu Glu Val Lys Ser Leu Lys Gln Glu Lys Glu Gln Val Ser Leu
            980                 985                 990
Arg Cys Arg Glu Leu Glu Ile Ile Ile Asn His Asn Arg Ala Glu Asn
        995                 1000                1005
Val Gln Ser Cys Asp Thr Gln Val Ser Ser Leu Leu Asp Gly Val Val
    1010                1015                1020
Thr Met Thr Ser Arg Gly Ala Glu Gly Ser Val Ser Lys Val Asn Lys
1025                1030                1035                1040
Ser Phe Gly Glu Glu Ser Lys Ile Met Val Glu Asp Lys Val Ser Phe
                1045                1050                1055
Glu Asn Met Thr Val Gly Glu Glu Ser Lys Gln Glu Gln Leu Ile Leu
            1060                1065                1070
Asp His Leu Pro Ser Val Thr Lys Glu Ser Ser Leu Arg Ala Thr Gln
        1075                1080                1085
Pro Ser Glu Asn Asp Lys Leu Gln Lys Glu Leu Asn Val Leu Lys Ser
    1090                1095                1100
Glu Gln Asn Asp Leu Arg Leu Gln Met Glu Ala Gln Arg Ile Cys Leu
1105                1110                1115                1120
Ser Leu Val Tyr Ser Thr His Val Asp Gln Val Arg Glu Tyr Met Glu
                1125                1130                1135
Asn Glu Lys Asp Lys Ala Leu Cys Ser Leu Lys Glu Glu Leu Ile Phe
            1140                1145                1150
Ala Gln Glu Glu Lys Ile Lys Glu Leu Gln Lys Ile His Gln Leu Glu
        1155                1160                1165
Leu Gln Thr Met Lys Thr Gln Glu Thr Gly Asp Glu Gly Lys Pro Leu
    1170                1175                1180
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His Leu Leu Ile Gly Lys Leu Gln Lys Ala Val Ser Glu Glu Cys Ser
1185 1190 1195 1200
Tyr Phe Leu Gln Thr Leu Cys Ser Val Leu Gly Glu Tyr Tyr Thr Pro
1205 1210 1215
Ala Leu Lys Cys Glu Val Asn Ala Glu Asp Lys Glu Asn Ser Gly Asp
1220 1225 1230
Tyr Ile Ser Glu Asn Glu Asp Pro Glu Leu Gln Asp Tyr Arg Tyr Glu
1235 1240 1245
Val Gln Asp Phe Gln Glu Asn Met His Thr Leu Leu Asn Lys Val Thr
1250 1255 1260
Glu Glu Tyr Asn Lys Leu Leu Val Leu Gln Thr Arg Leu Ser Lys Ile
1265 1270 1275 1280
Trp Gly Gln Gln Thr Asp Gly Met Lys Leu Glu Phe Gly Glu Glu Asn
1285 1290 1295
Leu Pro Lys Glu Glu Thr Glu Phe Leu Ser Ile His Ser Gln Met Thr
1300 1305 1310
Asn Leu Glu Asp Ile Asp Val Asn His Lys Ser Lys Leu Ser Ser Leu
1315 1320 1325
Gln Asp Leu Glu Lys Thr Lys Leu Glu Glu Gln Val Gln Glu Leu Glu
1330 1335 1340
Ser Leu Ile Ser Ser Leu Gln Gln Gln Leu Lys Glu Thr Glu Gln Asn
1345 1350 1355 1360
Tyr Glu Ala Glu Ile His Cys Leu Gln Lys Arg Leu Gln Ala Val Ser
1365 1370 1375
Glu Ser Thr Val Pro Pro Ser Leu Pro Val Asp Ser Val Val Ile Thr
1380 1385 1390
Glu Ser Asp Ala Gln Arg Thr Met Tyr Pro Gly Ser Cys Val Lys Lys
1395 1400 1405
Asn Ile Asp Gly Thr Ile Glu Phe Ser Gly Glu Phe Gly Val Lys Glu
1410 1415 1420
Glu Thr Asn Ile Val Lys Leu Leu Glu Lys Gln Tyr Gln Glu Gln Leu
1425 1430 1435 1440
Glu Glu Glu Val Ala Lys Val Ile Val Ser Met Ser Ile Ala Phe Ala
1445 1450 1455
Gln Gln Thr Glu Leu Ser Arg Ile Ser Gly Gly Lys Glu Asn Thr Ala
1460 1465 1470
Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe
1475 1480 1485
Asn Glu Met Lys Leu Ser Gln Asp Gln Ile Gly Phe Gln Thr Phe Glu
1490 1495 1500
Thr Val Asp Val Lys Phe Lys Glu Glu Phe Lys Pro Leu Ser Lys Glu
1505 1510 1515 1520
Leu Gly Glu His Gly Lys Glu Ile Leu Leu Ser Asn Ser Asp Pro His
1525 1530 1535
Asp Ile Pro Glu Ser Lys Asp Cys Val Leu Thr Ile Ser Glu Glu Met
1540 1545 1550
Phe Ser Lys Asp Lys Thr Phe Ile Val Arg Gln Ser Ile His Asp Glu
1555 1560 1565
Ile Ser Val Ser Ser Met Asp Ala Ser Arg Gln Leu Met Leu Asn Glu
1570 1575 1580
Glu Gln Leu Glu Asp Met Arg Gln Glu Leu Val Arg Gln Tyr Gln Glu
1585 1590 1595 1600
His Gln Gln Ala Thr Glu Leu Leu Arg Gln Ala His Met Arg Gln Met
1605 1610 1615
Glu Arg Gln Arg Glu Asp Gln Glu Gln Leu Gln Glu Glu Ile Lys Arg
1620 1625 1630
Leu Asn Arg Gln Leu Ala Gln Arg Ser Ser Ile Asp Asn Glu Asn Leu
1635 1640 1645
Val Ser Glu Arg Glu Arg Val Leu Leu Glu Glu Leu Glu Ala Leu Lys

    1650   1655   1660
Gln Leu Ser Leu Ala Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn
1665   1670   1675   1680
Ser Ser Thr Gln Thr Gln Asn Gly Asn Glu Asn Gln Gly Glu Val Glu
                1685   1690   1695
Glu Gln Thr Phe Lys Glu Lys Glu Leu Asp Arg Lys Pro Glu Asp Val
            1700   1705   1710
Pro Pro Glu Ile Leu Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn
        1715   1720   1725
Asn Arg Leu Leu Lys Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala
    1730   1735   1740
Val Glu Glu Thr Ile Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser
1745   1750   1755   1760
Ser Lys Ser Gln Ser Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu
                1765   1770   1775
Ala Ser Val Lys Ser Cys Val His Glu Glu His Thr Arg Val Thr Asp
            1780   1785   1790
Glu Ser Ile Pro Ser Tyr Ser Gly Ser Asp Met Pro Arg Asn Asp Ile
        1795   1800   1805
Asn Met Trp Ser Lys Val Thr Glu Glu Gly Thr Glu Leu Ser Gln Arg
    1810   1815   1820
Leu Val Arg Ser Gly Phe Ala Gly Thr Glu Ile Asp Pro Glu Asn Glu
1825   1830   1835   1840
Glu Leu Met Leu Asn Ile Ser Ser Arg Leu Gln Ala Ala Val Glu Lys
                1845   1850   1855
Leu Leu Glu Ala Ile Ser Glu Thr Ser Ser Gln Leu Glu His Ala Lys
            1860   1865   1870
Val Thr Gln Thr Glu Leu Met Arg Glu Ser Phe Arg Gln Lys Gln Glu
        1875   1880   1885
Ala Thr Glu Ser Leu Lys Cys Gln Glu Glu Leu Arg Glu Arg Leu His
    1890   1895   1900
Glu Glu Ser Arg Ala Arg Glu Gln Leu Ala Val Glu Leu Ser Lys Ala
1905   1910   1915   1920
Glu Gly Val Ile Asp Gly Tyr Ala Asp Glu Lys Thr Leu Phe Glu Arg
                1925   1930   1935
Gln Ile Gln Glu Lys Thr Asp Ile Ile Asp Arg Leu Glu Gln Glu Leu
            1940   1945   1950
Leu Cys Ala Ser Asn Arg Leu Gln Glu Leu Glu Ala Glu Gln Gln Gln
        1955   1960   1965
Ile Gln Glu Glu Arg Glu Leu Leu Ser Arg Gln Lys Glu Ala Met Lys
    1970   1975   1980
Ala Glu Ala Gly Pro Val Glu Gln Gln Leu Leu Gln Glu Thr Glu Lys
1985   1990   1995   2000
Leu Met Lys Glu Lys Leu Glu Val Gln Cys Gln Ala Glu Lys Val Arg
                2005   2010   2015
Asp Asp Leu Gln Lys Gln Val Lys Ala Leu Glu Ile Asp Val Glu Glu
            2020   2025   2030
Gln Val Ser Arg Phe Ile Glu Leu Glu Gln Glu Lys Asn Thr Glu Leu
        2035   2040   2045
Met Asp Leu Arg Gln Gln Asn Gln Ala Leu Glu Lys Gln Leu Glu Lys
    2050   2055   2060
Met Arg Lys Phe Leu Asp Glu Gln Ala Ile Asp Arg Glu His Glu Arg
2065   2070   2075   2080
Asp Val Phe Gln Gln Glu Ile Gln Lys Leu Glu Gln Gln Leu Lys Val
                2085   2090   2095
Val Pro Arg Phe Gln Pro Ile Ser Glu His Gln Thr Arg Glu Val Glu
            2100   2105   2110
Gln Leu Ala Asn His Leu Lys Glu Lys Thr Asp Lys Cys Ser Glu Leu
        2115   2120   2125

Leu Leu Ser Lys Glu Gln Leu Gln Arg Asp Ile Gln Glu Arg Asn Glu
2130 2135 2140
Glu Ile Glu Lys Leu Glu Phe Arg Val Arg Glu Leu Glu Gln Ala Leu
2145 2150 2155 2160
Leu Val Glu Asp Arg Lys His Phe Gly Ala Val Glu Ala Lys Pro Glu
2165 2170 2175
Leu Ser Leu Glu Val Gln Leu Gln Ala Glu Arg Asp Ala Ile Asp Arg
2180 2185 2190
Lys Glu Lys Glu Ile Thr Asn Leu Glu Glu Gln Leu Glu Gln Phe Arg
2195 2200 2205
Glu Glu Leu Glu Asn Lys Asn Glu Glu Val Gln Gln Leu His Met Gln
2210 2215 2220
Leu Glu Ile Gln Lys Lys Glu Ser Thr Thr Arg Leu Gln Glu Leu Glu
2225 2230 2235 2240
Gln Glu Asn Lys Leu Phe Lys Asp Asp Met Glu Lys Leu Gly Leu Ala
2245 2250 2255
Ile Lys Glu Ser Asp Ala Met Ser Thr Gln Asp Gln His Val Leu Phe
2260 2265 2270
Gly Lys Phe Ala Gln Ile Ile Gln Glu Lys Glu Val Glu Ile Asp Gln
2275 2280 2285
Leu Asn Glu Gln Val Thr Lys Leu Gln Gln Gln Leu Lys Ile Thr Thr
2290 2295 2300
Asp Asn Lys Val Ile Glu Glu Lys Asn Glu Leu Ile Arg Asp Leu Glu
2305 2310 2315 2320
Thr Gln Ile Glu Cys Leu Met Ser Asp Gln Glu Cys Val Lys Arg Asn
2325 2330 2335
Arg Glu Glu Glu Ile Glu Gln Leu Asn Glu Val Ile Glu Lys Leu Gln
2340 2345 2350
Gln Glu Leu Ala Asn Ile Gly Gln Lys Thr Ser Met Asn Ala His Ser
2355 2360 2365
Leu Ser Glu Glu Ala Asp Ser Leu Lys His Gln Leu Asp Val Val Ile
2370 2375 2380
Ala Glu Lys Leu Ala Leu Glu Gln Gln Val Glu Thr Ala Asn Glu Glu
2385 2390 2395 2400
Met Thr Phe Met Lys Asn Val Leu Lys Glu Thr Asn Phe Lys Met Asn
2405 2410 2415
Gln Leu Thr Gln Glu Leu Phe Ser Leu Lys Arg Glu Arg Glu Ser Val
2420 2425 2430
Glu Lys Ile Gln Ser Ile Pro Glu Asn Ser Val Asn Val Ala Ile Asp
2435 2440 2445
His Leu Ser Lys Asp Lys Pro Glu Leu Glu Val Val Leu Thr Glu Asp
2450 2455 2460
Ala Leu Lys Ser Leu Glu Asn Gln Thr Tyr Phe Lys Ser Phe Glu Glu
2465 2470 2475 2480
Asn Gly Lys Gly Ser Ile Ile Asn Leu Glu Thr Arg Leu Leu Gln Leu
2485 2490 2495
Glu Ser Thr Val Ser Ala Lys Asp Leu Glu Leu Thr Gln Cys Tyr Lys
2500 2505 2510
Gln Ile Lys Asp Met Gln Glu Gln Gly Gln Phe Glu Thr Glu Met Leu
2515 2520 2525
Gln Lys Lys Ile Val Asn Leu Gln Lys Ile Val Glu Glu Lys Val Ala
2530 2535 2540
Ala Ala Leu Val Ser Gln Ile Gln Leu Glu Ala Val Gln Glu Tyr Ala
2545 2550 2555 2560
Lys Phe Cys Gln Asp Asn Gln Thr Ile Ser Ser Glu Pro Glu Arg Thr
2565 2570 2575
Asn Ile Gln Asn Leu Asn Gln Leu Arg Glu Asp Glu Leu Gly Ser Asp
2580 2585 2590
Ile Ser Ala Leu Thr Leu Arg Ile Ser Glu Leu Glu Ser Gln Val Val

2595 2600 2605
Glu Met His Thr Ser Leu Ile Leu Glu Lys Glu Gln Val Glu Ile Ala
2610 2615 2620
Glu Lys Asn Val Leu Glu Lys Glu Lys Lys Leu Leu Glu Leu Gln Lys
2625 2630 2635 2640
Leu Leu Glu Gly Asn Glu Lys Lys Gln Arg Glu Lys Glu Lys Lys Arg
2645 2650 2655
Ser Pro Gln Asp Val Glu Val Leu Lys Thr Thr Thr Glu Leu Phe His
2660 2665 2670
Ser Asn Glu Glu Ser Gly Phe Phe Asn Glu Leu Glu Ala Leu Arg Ala
2675 2680 2685
Glu Ser Val Ala Thr Lys Ala Glu Leu Ala Ser Tyr Lys Glu Lys Ala
2690 2695 2700
Glu Lys Leu Gln Glu Glu Leu Leu Val Lys Glu Thr Asn Met Thr Ser
2705 2710 2715 2720
Leu Gln Lys Asp Leu Ser Gln Val Arg Asp His Leu Ala Glu Ala Lys
2725 2730 2735
Glu Lys Leu Ser Ile Leu Glu Lys Glu Asp Glu Thr Glu Val Gln Glu
2740 2745 2750
Ser Lys Lys Ala Cys Met Phe Glu Pro Leu Pro Ile Lys Leu Ser Lys
2755 2760 2765
Ser Ile Ala Ser Gln Thr Asp Gly Thr Leu Lys Ile Ser Ser Ser Asn
2770 2775 2780
Gln Thr Pro Gln Ile Leu Val Lys Asn Ala Gly Ile Gln Ile Asn Leu
2785 2790 2795 2800
Gln Ser Glu Cys Ser Ser Glu Glu Val Thr Glu Ile Ile Ser Gln Phe
2805 2810 2815
Thr Glu Lys Ile Glu Lys Met Gln Glu Leu His Ala Ala Glu Ile Leu
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Asp Met Glu Ser Arg His Ile Ser Glu Thr Glu Thr Leu Lys Arg Glu
2835 2840 2845
His Tyr Val Ala Val Gln Leu Leu Lys Glu Glu Cys Gly Thr Leu Lys
2850 2855 2860
Ala Val Ile Gln Cys Leu Arg Ser Lys Glu Gly Ser Ser Ile Pro Glu
2865 2870 2875 2880
Leu Ala His Ser Asp Ala Tyr Gln Thr Arg Glu Ile Cys Ser Ser Asp
2885 2890 2895
Ser Gly Ser Asp Trp Gly Gln Gly Ile Tyr Leu Thr His Ser Gln Gly
2900 2905 2910
Phe Asp Ile Ala Ser Glu Gly Arg Gly Glu Glu Ser Glu Ser Ala Thr
2915 2920 2925
Asp Ser Phe Pro Lys Lys Ile Lys Gly Leu Leu Arg Ala Val His Asn
2930 2935 2940
Glu Gly Met Gln Val Leu Ser Leu Thr Glu Ser Pro Tyr Ser Asp Gly
2945 2950 2955 2960
Glu Asp His Ser Ile Gln Gln Val Ser Glu Pro Trp Leu Glu Glu Arg
2965 2970 2975
Lys Ala Tyr Ile Asn Thr Ile Ser Ser Leu Lys Asp Leu Ile Thr Lys
2980 2985 2990
Met Gln Leu Gln Arg Glu Ala Glu Val Tyr Asp Ser Ser Gln Ser His
2995 3000 3005
Glu Ser Phe Ser Asp Trp Arg Gly Glu Leu Leu Leu Ala Leu Gln Gln
3010 3015 3020
Val Phe Leu Glu Glu Arg Ser Val Leu Leu Ala Ala Phe Arg Thr Glu
3025 3030 3035 3040
Leu Thr Ala Leu Gly Thr Thr Asp Ala Val Gly Leu Leu Asn Cys Leu
3045 3050 3055
Glu Gln Arg Ile Gln Glu Gln Gly Val Glu Tyr Gln Ala Ala Met Glu
3060 3065 3070

Cys Leu Gln Lys Ala Asp Arg Arg Ser Leu Leu Ser Glu Ile Gln Ala
3075 3080 3085
Leu His Ala Gln Met Asn Gly Arg Lys Ile Thr Leu Lys Arg Glu Gln
3090 3095 3100
Glu Ser Glu Lys Pro Ser Gln Glu Leu Leu Glu Tyr Asn Ile Gln Gln
3105 3110 3115 3120
Lys Gln Ser Gln Met Leu Glu Met Gln Val Glu Leu Ser Ser Met Lys
3125 3130 3135
Asp Arg Ala Thr Glu Leu Gln Glu Gln Leu Ser Ser Glu Lys Met Val
3140 3145 3150
Val Ala Glu Leu Lys Ser Glu Leu Ala Gln Thr Lys Leu Glu Leu Glu
3155 3160 3165
Thr Thr Leu Lys Ala Gln His Lys His Leu Lys Glu Leu Glu Ala Phe
3170 3175 3180
Arg Leu Glu Val Lys Asp Lys Thr Asp Glu Val His Leu Leu Asn Asp
3185 3190 3195 3200
Thr Leu Ala Ser Glu Gln Lys Lys Ser Arg Glu Leu Gln Trp Ala Leu
3205 3210 3215
Glu Lys Glu Lys Ala Lys Leu Gly Arg Ser Glu Glu Arg Asp Lys Glu
3220 3225 3230
Glu Leu Glu Asp Leu Lys Phe Ser Leu Glu Ser Gln Lys Gln Arg Asn
3235 3240 3245
Leu Gln Leu Asn Leu Leu Leu Glu Gln Gln Lys Gln Leu Leu Asn Glu
3250 3255 3260
Ser Gln Gln Lys Ile Glu Ser Gln Arg Met Leu Tyr Asp Ala Gln Leu
3265 3270 3275 3280
Ser Glu Glu Gln Gly Arg Asn Leu Glu Leu Gln Val Leu Leu Glu Ser
3285 3290 3295
Glu Lys Val Arg Ile Arg Glu Met Ser Ser Thr Leu Asp Arg Glu Arg
3300 3305 3310
Glu Leu His Ala Gln Leu Gln Ser Ser Asp Gly Thr Gly Gln Ser Arg
3315 3320 3325
Pro Pro Leu Pro Ser Glu Asp Leu Leu Lys Glu Leu Gln Lys Gln Leu
3330 3335 3340
Glu Glu Lys His Ser Arg Ile Val Glu Leu Leu Asn Glu Thr Glu Lys
3345 3350 3355 3360
Tyr Lys Leu Asp Ser Leu Gln Thr Arg Gln Gln Met Glu Lys Asp Arg
3365 3370 3375
Gln Val His Arg Lys Thr Leu Gln Thr Glu Gln Glu Ala Asn Thr Glu
3380 3385 3390
Gly Gln Lys Lys Met His Glu Leu Gln Ser Lys Val Glu Asp Leu Gln
3395 3400 3405
Arg Gln Leu Glu Glu Lys Arg Gln Gln Val Tyr Lys Leu Asp Leu Glu
3410 3415 3420
Gly Gln Arg Leu Gln Gly Ile Met Gln Glu Phe Gln Lys Gln Glu Leu
3425 3430 3435 3440
Glu Arg Glu Glu Lys Arg Glu Ser Arg Arg Ile Leu Tyr Gln Asn Leu
3445 3450 3455
Asn Glu Pro Thr Thr Trp Ser Leu Thr Ser Asp Arg Thr Arg Asn Trp
3460 3465 3470
Val Leu Gln Gln Lys Ile Glu Gly Glu Thr Lys Glu Ser Asn Tyr Ala
3475 3480 3485
Lys Leu Ile Glu Met Asn Gly Gly Gly Thr Gly Cys Asn His Glu Leu
3490 3495 3500
Glu Met Ile Arg Gln Lys Leu Gln Cys Val Ala Ser Lys Leu Gln Val
3505 3510 3515 3520
Leu Pro Gln Lys Ala Ser Glu Arg Leu Gln Phe Glu Thr Ala Asp Asp
3525 3530 3535
Glu Asp Phe Ile Trp Val Gln Glu Asn Ile Asp Glu Ile Ile Leu Gln

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            3540                3545                3550
Leu Gln Lys Leu Thr Gly Gln Gln Gly Glu Glu Pro Ser Leu Val Ser
        3555                3560                3565
Pro Ser Thr Ser Cys Gly Ser Leu Thr Glu Arg Leu Leu Arg Gln Asn
    3570                3575                3580
Ala Glu Leu Thr Gly His Ile Ser Gln Leu Thr Glu Glu Lys Asn Asp
3585                3590                3595                3600
Leu Arg Asn Met Val Met Lys Leu Glu Glu Gln Ile Arg Trp Tyr Arg
                3605                3610                3615
Gln Thr Gly Ala Gly Arg Asp Asn Ser Ser Arg Phe Ser Leu Asn Gly
            3620                3625                3630
Gly Ala Asn Ile Glu Ala Ile Ile Ala Ser Glu Lys Glu Val Trp Asn
        3635                3640                3645
Arg Glu Lys Leu Thr Leu Gln Lys Ser Leu Lys Arg Ala Glu Ala Glu
    3650                3655                3660
Val Tyr Lys Leu Lys Ala Glu Leu Arg Asn Asp Ser Leu Leu Gln Thr
3665                3670                3675                3680
Leu Ser Pro Asp Ser Glu His Val Thr Leu Lys Arg Ile Tyr Gly Lys
                3685                3690                3695
Tyr Leu Arg Ala Glu Ser Phe Arg Lys Ala Leu Ile Tyr Gln Lys Lys
            3700                3705                3710
Tyr Leu Leu Leu Leu Leu Gly Gly Phe Gln Glu Cys Glu Asp Ala Thr
        3715                3720                3725
Leu Ala Leu Leu Ala Arg Met Gly Gly Gln Pro Ala Phe Thr Asp Leu
    3730                3735                3740
Glu Val Ile Thr Asn Arg Pro Lys Gly Phe Thr Arg Phe Arg Ser Ala
3745                3750                3755                3760
Val Arg Val Ser Ile Ala Ile Ser Arg Met Lys Phe Leu Val Arg Arg
                3765                3770                3775
Trp His Arg Val Thr Gly Ser Val Ser Ile Asn Ile Asn Arg Asp Gly
            3780                3785                3790
Phe Gly Leu Asn Gln Gly Ala Glu Lys Thr Asp Ser Phe Tyr His Ser
        3795                3800                3805
Ser Gly Gly Leu Glu Leu Tyr Gly Glu Pro Arg His Thr Thr Tyr Arg
    3810                3815                3820
Ser Arg Ser Asp Leu Asp Tyr Ile Arg Ser Pro Leu Pro Phe Gln Asn
3825                3830                3835                3840
Arg Tyr Pro Gly Thr Pro Ala Asp Phe Asn Pro Gly Ser Leu Ala Cys
                3845                3850                3855
Ser Gln Leu Gln Asn Tyr Asp Pro Asp Arg Ala Leu Thr Asp Tyr Ile
            3860                3865                3870
Thr Arg Leu Glu Ala Leu Gln Arg Arg Leu Gly Thr Ile Gln Ser Gly
        3875                3880                3885
Ala Leu Ser Leu Thr Thr Ser Trp Gln His His Ser Ala Arg Pro Thr
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Ala Pro Leu Phe Phe Glu Ile Leu Ser His Ser Leu Gly
3905                3910                3915
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<212> DNA
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<211> 383
<212> PRT
<213> Homo sapiens

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35 40 45
Ser Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val
50 55 60

Ser Thr Gln Asn Leu Leu Leu Leu Leu Thr Asp Asn Glu Ala Trp Asn
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Gly Phe Val Ala Ala Ala Glu Leu Pro Arg Asn Glu Ala Asp Glu Leu
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Arg Lys Ala Leu Asp Asn Leu Ala Arg Gln Met Ile Met Lys Asp Lys
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Asn Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu
115 120 125
Phe Pro Arg Leu Lys Ser Lys Leu Glu Asp Asn Ile Arg Arg Leu Arg
130 135 140
Ala Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala
145 150 155 160
Asn Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu
165 170 175
Val Gly Met Gly Leu Ala Pro Phe Thr Glu Gly Gly Ser Leu Val Leu
180 185 190
Leu Glu Pro Gly Met Glu Leu Gly Ile Thr Ala Ala Leu Thr Gly Ile
195 200 205
Thr Ser Ser Thr Ile Asp Tyr Gly Lys Lys Trp Trp Thr Gln Ala Gln
210 215 220
Ala His Asp Leu Val Ile Lys Ser Leu Asp Lys Leu Lys Glu Val Lys
225 230 235 240
Glu Phe Leu Gly Glu Asn Ile Ser Asn Phe Leu Ser Leu Ala Gly Asn
245 250 255
Thr Tyr Gln Leu Thr Arg Gly Ile Gly Lys Asp Ile Arg Ala Leu Arg
260 265 270
Arg Ala Arg Ala Asn Leu Gln Ser Val Pro His Ala Ser Ala Ser Arg
275 280 285
Pro Arg Val Thr Glu Pro Ile Ser Ala Glu Ser Gly Glu Gln Val Glu
290 295 300
Arg Val Asn Glu Pro Ser Ile Leu Glu Met Ser Arg Gly Val Lys Leu
305 310 315 320
Thr Asp Val Ala Pro Val Ser Phe Phe Leu Val Leu Asp Val Val Tyr
325 330 335
Leu Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr
340 345 350
Ala Glu Glu Leu Lys Lys Val Ala Gln Glu Leu Glu Glu Lys Leu Asn
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Ile Leu Asn Asn Asn Tyr Lys Ile Leu Gln Ala Asp Gln Glu Leu
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<210> 11
<211> 3004
<212> DNA
<213> Homo sapiens

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<210> 12
<211> 414
<212> PRT
<213> *Homo sapiens*

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Ser Ala Leu Phe Leu Gly Val Arg Val Arg Ala Glu Glu Ala Gly Ala
35 40 45
Arg Val Gln Gln Asn Val Pro Ser Gly Thr Asp Thr Gly Asp Pro Gln
50 55 60
Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu Ser
65 70 75 80
Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val Ser
85 90 95

Thr Gln Asn Leu Leu Leu Leu Leu Thr Asp Asn Glu Ala Trp Asn Gly
100 105 110
Phe Val Ala Ala Ala Glu Leu Pro Arg Asn Glu Ala Asp Glu Leu Arg
115 120 125
Lys Ala Leu Asp Asn Leu Ala Arg Gln Met Ile Met Lys Asp Lys Asn
130 135 140
Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu Phe
145 150 155 160
Pro Arg Leu Lys Ser Lys Leu Glu Asp Asn Ile Arg Arg Leu Arg Ala
165 170 175
Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala Asn
180 185 190
Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu Val
195 200 205
Gly Met Gly Leu Ala Pro Phe Thr Glu Gly Gly Ser Leu Val Leu Leu
210 215 220
Glu Pro Gly Met Glu Leu Gly Ile Thr Ala Ala Leu Thr Gly Ile Thr
225 230 235 240
Ser Ser Thr Ile Asp Tyr Gly Lys Lys Trp Trp Thr Gln Ala Gln Ala
245 250 255
His Asp Leu Val Ile Lys Ser Leu Asp Lys Leu Lys Glu Val Lys Glu
260 265 270
Phe Leu Gly Glu Asn Ile Ser Asn Phe Leu Ser Leu Ala Gly Asn Thr
275 280 285
Tyr Gln Leu Thr Arg Gly Ile Gly Lys Asp Ile Arg Ala Leu Arg Arg
290 295 300
Ala Arg Ala Asn Leu Gln Ser Val Pro His Ala Ser Ala Ser Arg Pro
305 310 315 320
Arg Val Thr Glu Pro Ile Ser Ala Glu Ser Gly Glu Gln Val Glu Arg
325 330 335
Val Asn Glu Pro Ser Ile Leu Glu Met Ser Arg Gly Val Lys Leu Thr
340 345 350
Asp Val Ala Pro Val Ser Phe Phe Leu Val Leu Asp Val Val Tyr Leu
355 360 365
Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr Ala
370 375 380
Glu Glu Leu Lys Lys Val Ala Gln Glu Leu Glu Glu Lys Leu Asn Ile
385 390 395 400
Leu Asn Asn Asn Tyr Lys Ile Leu Gln Ala Asp Gln Glu Leu
405 410

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<211> 2298
<212> DNA
<213> Homo sapiens

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&lt;210&gt; 14
&lt;211&gt; 331
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 14
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            20                  25                  30
Glu Ala Trp Lys Arg Phe Val Thr Ala Ala Glu Leu Pro Arg Asp Glu
        35                  40                  45
Ala Asp Ala Leu Tyr Glu Ala Leu Lys Lys Leu Arg Thr Tyr Ala Ala
    50                  55                  60
Ile Glu Asp Glu Tyr Val Gln Gln Lys Asp Glu Gln Phe Arg Glu Trp
65                  70                  75                  80
Phe Leu Lys Glu Phe Pro Gln Val Lys Arg Lys Ile Gln Glu Ser Ile
                85                  90                  95
Glu Lys Leu Arg Ala Leu Ala Asn Gly Ile Glu Glu Val His Arg Gly
            100                 105                 110
Cys Thr Ile Ser Asn Val Val Ser Ser Ser Thr Gly Ala Ala Ser Gly
        115                 120                 125
Ile Met Ser Leu Ala Gly Leu Val Leu Ala Pro Phe Thr Ala Gly Thr
    130                 135                 140
Ser Leu Ala Leu Thr Ala Ala Gly Val Gly Leu Gly Ala Ala Ser Ala
145                 150                 155                 160
Val Thr Gly Ile Thr Thr Ser Ile Val Glu His Ser Tyr Thr Ser Ser
                165                 170                 175
Ala Glu Ala Glu Ala Ser Arg Leu Thr Ala Thr Ser Ile Asp Arg Leu
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Lys Val Phe Lys Glu Val Met Arg Asp Ile Thr Pro Asn Leu Leu Ser
        195                 200                 205
Leu Leu Asn Asn Tyr Tyr Glu Ala Thr Gln Thr Ile Gly Ser Glu Ile
    210                 215                 220
Arg Ala Ile Arg Gln Ala Arg Ala Arg Ala Arg Leu Pro Val Thr Thr
225                 230                 235                 240
Trp Arg Ile Ser Ala Gly Ser Gly Gly Gln Ala Glu Arg Thr Ile Ala
                245                 250                 255
Gly Thr Thr Arg Ala Val Ser Arg Gly Ala Arg Ile Leu Ser Ala Thr
            260                 265                 270
Thr Ser Gly Ile Phe Leu Ala Leu Asp Val Val Asn Leu Val Tyr Glu
        275                 280                 285
Ser Lys His Leu His Glu Gly Ala Lys Ser Ala Ser Ala Glu Glu Leu
    290                 295                 300
Arg Arg Gln Ala Gln Glu Leu Glu Glu Asn Leu Met Glu Leu Thr Gln
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Ile Tyr Gln Arg Leu Asn Pro Cys His Thr His
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<210> 15
<211> 1316
<212> DNA
<213> Homo sapiens

<400> 15

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<210> 16
<211> 265
<212> PRT
<213> Homo sapiens

<400> 16

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Glu Phe Leu Ala Thr Leu Ile Phe Val Phe Phe Gly Leu Gly Ser Ala
            20                  25                  30
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Leu Lys Trp Pro Ser Ala Leu Pro Thr Ile Leu Gln Ile Ala Leu Ala
        35   40   45
Phe Gly Leu Ala Ile Gly Thr Leu Ala Gln Ala Leu Gly Pro Val Ser
    50   55   60
Gly Gly His Ile Asn Pro Ala Ile Thr Leu Ala Leu Leu Val Gly Asn
65   70   75   80
Gln Ile Ser Leu Leu Arg Ala Phe Phe Tyr Val Ala Ala Gln Leu Val
                85   90   95
Gly Ala Ile Ala Gly Ala Gly Ile Leu Tyr Gly Val Ala Pro Leu Asn
            100   105   110
Ala Arg Gly Asn Leu Ala Val Asn Ala Leu Asn Asn Asn Thr Thr Gln
        115   120   125
Gly Gln Ala Met Val Val Glu Leu Ile Leu Thr Phe Gln Leu Ala Leu
    130   135   140
Cys Ile Phe Ala Ser Thr Asp Ser Arg Arg Thr Ser Pro Val Gly Ser
145   150   155   160
Pro Ala Leu Ser Ile Gly Leu Ser Val Thr Leu Gly His Leu Val Gly
                165   170   175
Ile Tyr Phe Thr Gly Cys Ser Met Asn Pro Ala Arg Ser Phe Gly Pro
            180   185   190
Ala Val Val Met Asn Arg Phe Ser Pro Ala His Trp Val Phe Trp Val
        195   200   205
Gly Pro Ile Val Gly Ala Val Leu Ala Ala Ile Leu Tyr Phe Tyr Leu
    210   215   220
Leu Phe Pro Asn Ser Leu Ser Leu Ser Glu Arg Val Ala Ile Ile Lys
225   230   235   240
Gly Thr Tyr Glu Pro Asp Glu Asp Trp Glu Glu Gln Arg Glu Glu Arg
                245   250   255
Lys Lys Thr Met Glu Leu Thr Thr Arg
            260   265

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<211> 1258
<212> DNA
<213> Homo sapiens

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aagatgagct tttgaatata agttgtctgc tagatcatgg tttgtattga actaacaagg 180
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<210> 18
<211> 22
<212> PRT
<213> Homo sapiens

<400> 18
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Lys Leu Phe Asp Ser Tyr
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<210> 19
<211> 983
<212> DNA
<213> Homo sapiens

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<211> 180
<212> PRT
<213> Homo sapiens

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Ile Ile Val Ile Leu Gly Val Pro Leu Ile Ile Phe Thr Ile Lys Ala
35 40 45
Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg
50 55 60
Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly
65 70 75 80
Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
85 90 95
Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
100 105 110
Val Glu Glu Leu Glu Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln
115 120 125

Asp Ala Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val Leu
    130   135   140
Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser Ser Gln Asp Ser
145   150   155   160
Ser Ser Ala Ala Ala Pro Gln Leu Leu Ile Val Leu Leu Gly Leu Ser
                165   170   175
Ala Leu Leu Gln
            180

<210> 21
<211> 4859
<212> DNA
<213> *Homo sapiens*

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<210> 22
<211> 244
<212> PRT
<213> Homo sapiens

<400> 22
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Ser Ile Ser Asn Arg Ala Ala Val Pro Glu His Gly Val Ala Pro Asp
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Ala Glu Arg Leu Arg Leu Pro Glu Arg Glu Val Thr Lys Glu His Gly
35 40 45
Asp Pro Gly Asp Thr Trp Lys Asp Tyr Cys Thr Leu Val Thr Ile Ala
50 55 60
Lys Ser Leu Leu Asp Leu Asn Lys Tyr Arg Pro Ile Gln Thr Pro Ser
65 70 75 80
Val Cys Ser Asp Ser Leu Glu Ser Pro Asp Glu Asp Met Gly Ser Asp
85 90 95
Ser Asp Val Thr Thr Glu Ser Gly Ser Ser Pro Ser His Ser Pro Glu
100 105 110

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Glu Arg Gln Asp Pro Gly Ser Ala Pro Ser Pro Leu Ser Leu Leu His
        115                 120                 125
Pro Gly Val Ala Ala Lys Gly Lys His Ala Ser Glu Lys Arg His Lys
    130                 135                 140
Cys Pro Tyr Ser Gly Cys Gly Lys Val Tyr Gly Lys Ser Ser His Leu
145                 150                 155                 160
Lys Ala His Tyr Arg Val His Thr Gly Glu Arg Pro Phe Pro Cys Thr
                165                 170                 175
Trp Pro Asp Cys Leu Lys Lys Phe Ser Arg Ser Asp Glu Leu Thr Arg
            180                 185                 190
His Tyr Arg Thr His Thr Gly Glu Lys Gln Phe Arg Cys Pro Leu Cys
        195                 200                 205
Glu Lys Arg Phe Met Arg Ser Asp His Leu Thr Lys His Ala Arg Arg
    210                 215                 220
His Thr Glu Phe His Pro Ser Met Ile Lys Arg Ser Lys Lys Ala Leu
225                 230                 235                 240
Ala Asn Ala Leu
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<210> 23
<211> 1304
<212> DNA
<213> Homo sapiens

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<210> 24
<211> 232
<212> PRT
<213> Homo sapiens

<400> 24
Met His Arg Arg Arg Ser Arg Ser Cys Arg Glu Asp Gln Lys Pro Val
 1               5                  10                  15
Met Asp Asp Gln Arg Asp Leu Ile Ser Asn Asn Glu Gln Leu Pro Met
            20                  25                  30
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Leu Gly Arg Arg Pro Gly Ala Pro Glu Ser Lys Cys Ser Arg Gly Ala
        35                  40                  45
Leu Tyr Thr Gly Phe Ser Ile Leu Val Thr Leu Leu Leu Ala Gly Gln
    50                  55                  60
Ala Thr Thr Ala Tyr Phe Leu Tyr Gln Gln Gln Gly Arg Leu Asp Lys
65                  70                  75                  80
Leu Thr Val Thr Ser Gln Asn Leu Gln Leu Glu Asn Leu Arg Met Lys
                85                  90                  95
Leu Pro Lys Pro Pro Lys Pro Val Ser Lys Met Arg Met Ala Thr Pro
            100                 105                 110
Leu Leu Met Gln Ala Leu Pro Met Gly Ala Leu Pro Gln Gly Pro Met
        115                 120                 125
Gln Asn Ala Thr Lys Tyr Gly Asn Met Thr Glu Asp His Val Met His
    130                 135                 140
Leu Leu Gln Asn Ala Asp Pro Leu Lys Val Tyr Pro Pro Leu Lys Gly
145                 150                 155                 160
Ser Phe Pro Glu Asn Leu Arg His Leu Lys Asn Thr Met Glu Thr Ile
                165                 170                 175
Asp Trp Lys Val Phe Glu Ser Trp Met His His Trp Leu Leu Phe Glu
            180                 185                 190
Met Ser Arg His Ser Leu Glu Gln Lys Pro Thr Asp Ala Pro Pro Lys
        195                 200                 205
Glu Ser Leu Glu Leu Glu Asp Pro Ser Ser Gly Leu Gly Val Thr Lys
    210                 215                 220
Gln Asp Leu Gly Pro Val Pro Met
225                 230


<210> 25
<211> 1615
<212> DNA
<213> Homo sapiens

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<210> 26
<211> 499
<212> PRT
<213> Homo sapiens

<400> 26
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            20                  25                  30
Lys Glu Ala Ala Gly Pro Ala Pro Ser Pro Met Arg Ala Ala Asn Arg
        35                  40                  45
Ser His Ser Ala Gly Arg Thr Pro Gly Arg Thr Pro Gly Lys Ser Ser
    50                  55                  60
Ser Lys Val Gln Thr Thr Pro Ser Lys Pro Gly Gly Asp Arg Tyr Ile
65                  70                  75                  80
Pro His Arg Ser Ala Ala Gln Met Glu Val Ala Ser Phe Leu Leu Ser
                85                  90                  95
Lys Glu Asn Gln Pro Glu Asn Ser Gln Thr Pro Thr Lys Lys Glu His
            100                 105                 110
Gln Lys Ala Trp Ala Leu Asn Leu Asn Gly Phe Asp Val Glu Glu Ala
        115                 120                 125
Lys Ile Leu Arg Leu Ser Gly Lys Pro Gln Asn Ala Pro Glu Gly Tyr
    130                 135                 140
Gln Asn Arg Leu Lys Val Leu Tyr Ser Gln Lys Ala Thr Pro Gly Ser
145                 150                 155                 160
Ser Arg Lys Thr Cys Arg Tyr Ile Pro Ser Leu Pro Asp Arg Ile Leu
                165                 170                 175
Asp Ala Pro Glu Ile Arg Asn Asp Tyr Tyr Leu Asn Leu Val Asp Trp
            180                 185                 190
Ser Ser Gly Asn Val Leu Ala Val Ala Leu Asp Asn Ser Val Tyr Leu
        195                 200                 205
Trp Ser Ala Ser Ser Gly Asp Ile Leu Gln Leu Leu Gln Met Glu Gln
    210                 215                 220
Pro Gly Glu Tyr Ile Ser Ser Val Ala Trp Ile Lys Glu Gly Asn Tyr
225                 230                 235                 240
Leu Ala Val Gly Thr Ser Ser Ala Glu Val Gln Leu Trp Asp Val Gln
                245                 250                 255
Gln Gln Lys Arg Leu Arg Asn Met Thr Ser His Ser Ala Arg Val Gly
            260                 265                 270
Ser Leu Ser Trp Asn Ser Tyr Ile Leu Ser Ser Gly Ser Arg Ser Gly
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His Ile His His His Asp Val Arg Val Ala Glu His His Val Ala Thr
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Leu Ser Gly His Ser Gln Glu Val Cys Gly Leu Arg Trp Ala Pro Asp
305                 310                 315                 320
Gly Arg His Leu Ala Ser Gly Gly Asn Asp Asn Leu Val Asn Val Trp
                325                 330                 335
Pro Ser Ala Pro Gly Glu Gly Gly Trp Val Pro Leu Gln Thr Phe Thr
            340                 345                 350
Gln His Gln Gly Ala Val Lys Ala Val Ala Trp Cys Pro Trp Gln Ser
        355                 360                 365
Asn Val Leu Ala Thr Gly Gly Gly Thr Ser Asp Arg His Ile Arg Ile
    370                 375                 380
Trp Asn Val Cys Ser Gly Ala Cys Leu Ser Ala Val Asp Ala His Ser
385                 390                 395                 400
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Gln Val Cys Ser Ile Leu Trp Ser Pro His Tyr Lys Glu Leu Ile Ser
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Gly His Gly Phe Ala Gln Asn Gln Leu Val Ile Trp Lys Tyr Pro Thr
420 425 430
Met Ala Lys Val Ala Glu Leu Lys Gly His Thr Ser Arg Val Leu Ser
435 440 445
Leu Thr Met Ser Pro Asp Gly Ala Thr Val Ala Ser Ala Ala Ala Asp
450 455 460
Glu Thr Leu Arg Leu Trp Arg Cys Phe Glu Leu Asp Pro Ala Arg Arg
465 470 475 480
Arg Glu Arg Glu Lys Ala Ser Ala Ala Lys Ser Ser Leu Ile His Gln
485 490 495
Gly Ile Arg

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<212> DNA
<213> Homo sapiens

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<211> 168
<212> PRT
<213> Homo sapiens

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35 40 45
Asn Pro Glu Ile Ala Arg Arg Leu Leu Leu Arg Gly Ala Asn Pro Asp
50 55 60
Leu Lys Asp Arg Thr Gly Phe Ala Val Ile His Asp Ala Ala Arg Ala
65 70 75 80
Gly Phe Leu Asp Thr Leu Gln Thr Leu Leu Glu Phe Gln Ala Asp Val
85 90 95
Asn Ile Glu Asp Asn Glu Gly Asn Leu Pro Leu His Leu Ala Ala Lys
100 105 110
Glu Gly His Leu Arg Val Val Glu Phe Leu Val Lys His Thr Ala Ser
115 120 125
Asn Val Gly His Arg Asn His Lys Gly Asp Thr Ala Cys Asp Leu Ala
130 135 140
Arg Leu Tyr Gly Arg Asn Glu Val Val Ser Leu Met Gln Ala Asn Gly
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Ala Gly Gly Ala Thr Asn Leu Gln
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<210> 29
<211> 4049
<212> DNA
<213> Homo sapiens

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<210> 30
<211> 184
<212> PRT
<213> Homo sapiens

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Thr Leu Leu Pro Ala Ala Glu Gly Lys Lys Lys Gly Ser Gln Gly Ala
20 25 30
Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln
35 40 45
Ser Pro Gln Gln Pro Gly Ser Arg Asn Arg Gly Arg Gly Gln Gly Arg

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Gly Thr Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser Gln Glu Ala
65                  70                  75                  80
Leu His Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp Cys Lys Thr
                85                  90                  95
Gln Pro Leu Lys Gln Thr Ile His Glu Glu Gly Cys Asn Ser Arg Thr
            100                 105                 110
Ile Ile Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe Tyr Ile Pro
        115                 120                 125
Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys
    130                 135                 140
Lys Pro Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn Cys Pro Glu
145                 150                 155                 160
Leu Gln Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val Lys Gln Cys
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Arg Cys Ile Ser Ile Asp Leu Asp
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<210> 31
<211> 3443
<212> DNA
<213> Homo sapiens

<400> 31

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<210> 32
<211> 211
<212> PRT
<213> Homo sapiens

<400> 32
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Tyr Ser Tyr Ala Gly Asp Asn Ile Val Thr Ala Gln Ala Met Tyr Glu
35 40 45
Gly Leu Trp Met Ser Cys Val Ser Gln Ser Thr Gly Gln Ile Gln Cys
50 55 60
Lys Val Phe Asp Ser Leu Leu Asn Leu Ser Ser Thr Leu Gln Ala Thr
65 70 75 80
Arg Ala Leu Met Val Val Gly Ile Leu Leu Gly Val Ile Ala Ile Phe
85 90 95
Val Ala Thr Val Gly Met Lys Cys Met Lys Cys Leu Glu Asp Asp Glu
100 105 110
Val Gln Lys Met Arg Met Ala Val Ile Gly Gly Ala Ile Phe Leu Leu
115 120 125
Ala Gly Leu Ala Ile Leu Val Ala Thr Ala Trp Tyr Gly Asn Arg Ile
130 135 140
Val Gln Glu Phe Tyr Asp Pro Met Thr Pro Val Asn Ala Arg Tyr Glu
145 150 155 160
Phe Gly Gln Ala Leu Phe Thr Gly Trp Ala Ala Ala Ser Leu Cys Leu
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210

<210> 33
<211> 4318
<212> DNA
<213> Homo sapiens

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Glu Arg Gly Pro Pro Gly Pro Met Gly Pro Pro Gly Leu Ala Gly Pro
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Pro Ala Gly Pro Pro Gly Ala Pro Gly Ala Pro Gly Ala Pro Gly Pro
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Val Gly Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Thr Gly Pro Ala
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Gly Pro Ala Gly Pro Val Gly Pro Val Gly Ala Arg Gly Pro Ala Gly
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Arg Gly Ile Lys Gly His Arg Gly Phe Ser Gly Leu Gln Gly Pro Pro
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Asp Gly Leu Asn Gly Leu Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg
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Thr Thr Leu Lys Ser Leu Ser Gln Gln Ile Glu Asn Ile Arg Ser Pro
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Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Lys Met
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Cys His Ser Asp Trp Lys Ser Gly Glu Tyr Trp Ile Asp Pro Asn Gln
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Gly Cys Asn Leu Asp Ala Ile Lys Val Phe Cys Asn Met Glu Thr Gly
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Glu Thr Cys Val Tyr Pro Thr Gln Pro Ser Val Ala Gln Lys Asn Trp
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Tyr Ile Ser Lys Asn Pro Lys Asp Lys Arg His Val Trp Phe Gly Glu
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Glu Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Val Ala Tyr
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Ser Asn Glu Ile Glu Ile Arg Ala Glu Gly Asn Ser Arg Phe Thr Tyr
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Ser Val Thr Val Asp Gly Cys Thr Ser His Thr Gly Ala Trp Gly Lys
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<213> Homo sapiens

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<212> PRT
<213> Homo sapiens

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35 40 45
Pro Pro Gly Arg Asp Gly Glu Asp Gly Pro Thr Gly Pro Pro Gly Pro
50 55 60
Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala Ala Gln
65 70 75 80
Tyr Asp Gly Lys Gly Val Gly Leu Gly Pro Gly Pro Met Gly Leu Met
85 90 95
Gly Pro Arg Gly Pro Pro Gly Ala Ala Gly Ala Pro Gly Pro Gln Gly
100 105 110
Phe Gln Gly Pro Ala Gly Glu Pro Gly Glu Pro Gly Gln Thr Gly Pro
115 120 125
Ala Gly Ala Arg Gly Pro Ala Gly Pro Pro Gly Lys Ala Gly Glu Asp
130 135 140
Gly His Pro Gly Lys Pro Gly Arg Pro Gly Glu Arg Gly Val Val Gly
145 150 155 160
Pro Gln Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Phe
165 170 175
Lys Gly Ile Arg Gly His Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro
180 185 190
Gly Ala Pro Gly Val Lys Gly Glu Pro Gly Ala Pro Gly Glu Asn Gly
195 200 205
Thr Pro Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg
210 215 220
Val Gly Ala Pro Gly Pro Ala Gly Ala Arg Gly Ser Asp Gly Ser Val
225 230 235 240
Gly Pro Val Gly Pro Ala Gly Pro Ile Gly Ser Ala Gly Pro Pro Gly
245 250 255
Phe Pro Gly Ala Pro Gly Pro Lys Gly Glu Ile Gly Ala Val Gly Asn
260 265 270
Ala Gly Pro Ala Gly Pro Ala Gly Pro Arg Gly Glu Val Gly Leu Pro
275 280 285
Gly Leu Ser Gly Pro Val Gly Pro Pro Gly Asn Pro Gly Ala Asn Gly
290 295 300
Leu Thr Gly Ala Lys Gly Ala Ala Gly Leu Pro Gly Val Ala Gly Ala
305 310 315 320
Pro Gly Leu Pro Gly Pro Arg Gly Ile Pro Gly Pro Val Gly Ala Ala
325 330 335
Gly Ala Thr Gly Ala Arg Gly Leu Val Gly Glu Pro Gly Pro Ala Gly
340 345 350
Ser Lys Gly Glu Ser Gly Asn Lys Gly Glu Pro Gly Ser Ala Gly Pro
355 360 365
Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn
370 375 380
Gly Glu Ala Gly Ser Ala Gly Pro Pro Gly Pro Pro Gly Leu Arg Gly
385 390 395 400
Ser Pro Gly Ser Arg Gly Leu Pro Gly Ala Asp Gly Arg Ala Gly Val
405 410 415
Met Gly Pro Pro Gly Ser Arg Gly Ala Ser Gly Pro Ala Gly Val Arg
420 425 430

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Gly Pro Asn Gly Asp Ala Gly Arg Pro Gly Glu Pro Gly Leu Met Gly
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Pro Arg Gly Leu Pro Gly Ser Pro Gly Asn Ile Gly Pro Ala Gly Lys
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Glu Gly Pro Val Gly Leu Pro Gly Ile Asp Gly Arg Pro Gly Pro Ile
465                 470                 475                 480
Gly Pro Ala Gly Ala Arg Gly Glu Pro Gly Asn Ile Gly Phe Pro Gly
                485                 490                 495
Pro Lys Gly Pro Thr Gly Asp Pro Gly Lys Asn Gly Asp Lys Gly His
            500                 505                 510
Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn
        515                 520                 525
Gly Ala Gln Gly Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly
    530                 535                 540
Glu Gln Gly Pro Ala Gly Pro Pro Gly Phe Gln Gly Leu Pro Gly Pro
545                 550                 555                 560
Ser Gly Pro Ala Gly Glu Val Gly Lys Pro Gly Glu Arg Gly Leu His
                565                 570                 575
Gly Glu Phe Gly Leu Pro Gly Pro Ala Gly Pro Arg Gly Glu Arg Gly
            580                 585                 590
Pro Pro Gly Glu Ser Gly Ala Ala Gly Pro Thr Gly Pro Ile Gly Ser
        595                 600                 605
Arg Gly Pro Ser Gly Pro Pro Gly Pro Asp Gly Asn Lys Gly Glu Pro
    610                 615                 620
Gly Val Val Gly Ala Val Gly Thr Ala Gly Pro Ser Gly Pro Ser Gly
625                 630                 635                 640
Leu Pro Gly Glu Arg Gly Ala Ala Gly Ile Pro Gly Gly Lys Gly Glu
                645                 650                 655
Lys Gly Glu Pro Gly Leu Arg Gly Glu Ile Gly Asn Pro Gly Arg Asp
            660                 665                 670
Gly Ala Arg Gly Ala His Gly Ala Val Gly Ala Pro Gly Pro Ala Gly
        675                 680                 685
Ala Thr Gly Asp Arg Gly Glu Ala Gly Ala Ala Gly Pro Ala Gly Pro
    690                 695                 700
Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg Gly Glu Val Gly Pro Ala
705                 710                 715                 720
Gly Pro Asn Gly Phe Ala Gly Pro Ala Gly Ala Ala Gly Gln Pro Gly
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Ala Lys Gly Glu Arg Gly Ala Lys Gly Pro Lys Gly Glu Asn Gly Val
            740                 745                 750
Val Gly Pro Thr Gly Pro Val Gly Ala Ala Gly Pro Ala Gly Pro Asn
        755                 760                 765
Gly Pro Pro Gly Pro Ala Gly Ser Arg Gly Asp Gly Gly Pro Pro Gly
    770                 775                 780
Met Thr Gly Phe Pro Gly Ala Ala Gly Arg Thr Gly Pro Pro Gly Pro
785                 790                 795                 800
Ser Gly Ile Ser Gly Pro Pro Gly Pro Pro Gly Pro Ala Gly Lys Glu
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Gly Leu Arg Gly Pro Arg Gly Asp Gln Gly Pro Val Gly Arg Thr Gly
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Glu Val Gly Ala Val Gly Pro Pro Gly Phe Ala Gly Glu Lys Gly Pro
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Ser Gly Glu Ala Gly Thr Ala Gly Pro Pro Gly Thr Pro Gly Pro Gln
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Gly Leu Leu Gly Ala Pro Gly Ile Leu Gly Leu Pro Gly Ser Arg Gly
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Glu Arg Gly Leu Pro Gly Val Ala Gly Ala Val Gly Glu Pro Gly Pro
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Lys Gly Glu Arg Gly Tyr Pro Gly Asn Ile Gly Pro Val Gly Ala Ala
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Gly Ala Pro Gly Pro His Gly Pro Val Gly Pro Ala Gly Lys His Gly
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Asn Arg Gly Glu Thr Gly Pro Ser Gly Pro Val Gly Pro Ala Gly Ala
            980                 985                 990
Val Gly Pro Arg Gly Pro Ser Gly Pro Gln Gly Ile Arg Gly Asp Lys
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Gly Glu Pro Gly Glu Lys Gly Pro Arg Gly Leu Pro Gly Leu Lys Gly
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His Asn Gly Leu Gln Gly Leu Pro Gly Ile Ala Gly His His Gly Asp
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Thr Val Gly Pro Ala Gly Ile Arg Gly Pro Gln Gly His Gln Gly Pro
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Ala Thr Leu Lys Ser Leu Asn Asn Gln Ile Glu Thr Leu Leu Thr Pro
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Gly Cys Thr Met Asp Ala Ile Lys Val Tyr Cys Asp Phe Ser Thr Gly
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Glu Thr Cys Ile Arg Ala Gln Pro Glu Asn Ile Pro Ala Lys Asn Trp
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Tyr Arg Ser Ser Lys Asp Lys Lys His Val Trp Leu Gly Glu Thr Ile
            1220                1225                1230
Asn Ala Gly Ser Gln Phe Glu Tyr Asn Val Glu Gly Val Thr Ser Lys
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Glu Met Ala Thr Gln Leu Ala Phe Met Arg Leu Leu Ala Asn Tyr Ala
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Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile Ala Tyr Met Asp
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Glu Glu Thr Gly Asn Leu Lys Lys Ala Val Ile Leu Gln Gly Ser Asn
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Asp Val Glu Leu Val Ala Glu Gly Asn Ser Arg Phe Thr Tyr Thr Val
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Leu Val Asp Gly Cys Ser Lys Lys Thr Asn Glu Trp Gly Lys Thr Ile
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Ile Glu Tyr Lys Thr Asn Lys Pro Ser Arg Leu Pro Phe Leu Asp Ile
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35 40 45

Pro Gln Tyr Gln Pro Leu Gly Gln Gln Val Pro His Met Pro Leu Ala
50 55 60
Lys Asp Gly Leu Ala Met Gly Lys Glu Met Pro His Leu Gln Tyr Gly
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Lys Glu Tyr Pro His Leu Pro Gln Tyr Met Lys Glu Ile Gln Pro Ala
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Pro Arg Met Gly Lys Glu Ala Val Pro Lys Lys Gly Lys Glu Ile Pro
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Leu Ala Ser Leu Arg Gly Glu Gln Gly Pro Arg Gly Glu Pro Gly Pro
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Arg Gly Pro Pro Gly Pro Pro Gly Leu Pro Gly His Gly Ile Pro Gly
130 135 140
Ile Lys Gly Lys Pro Gly Pro Gln Gly Tyr Pro Gly Val Gly Lys Pro
145 150 155 160
Gly Met Pro Gly Met Pro Gly Lys Pro Gly Ala Met Gly Met Pro Gly
165 170 175
Ala Lys Gly Glu Ile Gly Gln Lys Gly Glu Ile Gly Pro Met Gly Ile
180 185 190
Pro Gly Pro Gln Gly Pro Pro Gly Pro His Gly Leu Pro Gly Ile Gly
195 200 205
Lys Pro Gly Gly Pro Gly Leu Pro Gly Gln Pro Gly Pro Lys Gly Asp
210 215 220
Arg Gly Pro Lys Gly Leu Pro Gly Pro Gln Gly Leu Arg Gly Pro Lys
225 230 235 240
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245 250 255
Pro Gly Met His Gly Leu Pro Gly Pro Val Gly Leu Pro Gly Val Gly
260 265 270
Lys Pro Gly Val Thr Gly Phe Pro Gly Pro Gln Gly Pro Leu Gly Lys
275 280 285
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Gly Val Gln Gly Pro Pro Gly Ile Pro Gly Ile Gly Lys Pro Gly Gln
305 310 315 320
Asp Gly Ile Pro Gly Gln Pro Gly Phe Pro Gly Gly Lys Gly Glu Gln
325 330 335
Gly Leu Pro Gly Leu Pro Gly Ala Pro Gly Leu Pro Gly Ile Gly Lys
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Gly Ala Leu Gly Pro Arg Gly Glu Lys Gly Pro Ile Gly Ser Pro Gly
370 375 380
Ile Gly Gly Ser Pro Gly Glu Pro Gly Leu Pro Gly Ile Pro Gly Pro
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405 410 415
Gly Ile Val Gly Pro Gln Gly Pro Pro Gly Pro Lys Gly Glu Pro Gly
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Leu Gln Gly Phe Pro Gly Lys Pro Gly Phe Leu Gly Glu Val Gly Pro
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Pro Gly Met Arg Gly Phe Pro Gly Pro Ile Gly Pro Lys Gly Glu His
450 455 460
Gly Gln Lys Gly Val Pro Gly Leu Pro Gly Val Pro Gly Leu Leu Gly
465 470 475 480
Pro Lys Gly Glu Pro Gly Ile Pro Gly Asp Gln Gly Leu Gln Gly Pro
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Thr Pro Pro Pro Gln Gly Glu Tyr Leu Pro Asp Met Gly Leu Gly Ile
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Asp Gly Val Lys Pro Pro His Ala Thr Gly Ala Lys Lys Gly Lys Asn
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Gly Gly Pro Ala Tyr Glu Met Pro Ala Phe Thr Ala Glu Leu Thr Ala
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Pro Phe Pro Pro Val Gly Gly Pro Val Lys Phe Asn Lys Leu Leu Tyr
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Val Pro Gly Val Tyr Tyr Phe Ala Tyr His Val His Cys Lys Gly Gly
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Tyr Asp Glu Tyr Lys Lys Gly Phe Leu Asp Gln Ala Ser Gly Ser Ala
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Val Leu Leu Leu Arg Pro Gly Asp Arg Val Phe Leu Gln Met Pro Ser
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<211> 5064
<212> DNA
<213> Homo sapiens

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<212> PRT
<213> Homo sapiens

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35 40 45
Glu His Asp Gly Pro Val Arg Gly Ile Asp Phe His Lys Gln Gln Pro
50 55 60
Leu Phe Val Ser Gly Gly Asp Asp Tyr Lys Ile Lys Val Trp Asn Tyr
65 70 75 80
Lys Leu Arg Arg Cys Leu Phe Thr Leu Leu Gly His Leu Asp Tyr Ile
85 90 95
Arg Thr Thr Phe Phe His His Glu Tyr Pro Trp Ile Leu Ser Ala Ser
100 105 110
Asp Asp Gln Thr Ile Arg Val Trp Asn Trp Gln Ser Arg Thr Cys Val
115 120 125
Cys Val Leu Thr Gly His Asn His Tyr Val Met Cys Ala Gln Phe His
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Pro Thr Glu Asp Leu Val Val Ser Ala Ser Leu Asp Gln Thr Val Arg
145 150 155 160
Val Trp Asp Ile Ser Gly Leu Arg Lys Lys Asn Leu Ser Pro Gly Ala
165 170 175
Val Glu Ser Asp Val Arg Gly Ile Thr Gly Val Asp Leu Phe Gly Thr
180 185 190
Thr Asp Ala Val Val Lys His Val Leu Glu Gly His Asp Arg Gly Val
195 200 205
Asn Trp Ala Ala Phe His Pro Thr Met Pro Leu Ile Val Ser Gly Ala
210 215 220
Asp Asp Arg Gln Val Lys Ile Trp Arg Met Asn Glu Ser Lys Ala Trp
225 230 235 240
Glu Val Asp Thr Cys Arg Gly His Tyr Asn Asn Val Ser Cys Ala Val
245 250 255
Phe His Pro Arg Gln Glu Leu Ile Leu Ser Asn Ser Glu Asp Lys Ser
260 265 270
Ile Arg Val Trp Asp Met Ser Lys Arg Thr Gly Val Gln Thr Phe Arg
275 280 285
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290 295 300
Leu Phe Ala Ala Gly His Asp Gly Gly Met Ile Val Phe Lys Leu Glu
305 310 315 320
Arg Glu Arg Pro Ala Tyr Ala Val His Gly Asn Met Leu His Tyr Val
325 330 335
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Ala Val Met Gln Leu Arg Ser Gly Ser Lys Phe Pro Val Phe Asn Met
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Ser Tyr Asn Pro Ala Glu Asn Ala Val Leu Leu Cys Thr Arg Ala Ser
370 375 380

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405 410 415
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His Ser Leu Leu Ile Lys Asn Leu Lys Asn Glu Ile Thr Lys Lys Val
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Gln Val Pro Asn Cys Asp Glu Ile Phe Tyr Ala Gly Thr Gly Asn Leu
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465 470 475 480
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485 490 495
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Arg Val Lys Ser Gly Ala Trp Asp Glu Ser Gly Val Phe Ile Tyr Thr
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Ile Arg Thr Leu Asp Leu Pro Ile Tyr Val Thr Arg Val Lys Gly Asn
565 570 575
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Asp Glu Val Leu His Met Val Arg Asn Ala Lys Leu Val Gly Gln Ser
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Gly Gln Lys Ser Leu Ala Tyr Leu Thr Ala Ala Thr His Gly Leu Asp
755 760 765
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785 790 795 800
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835 840 845
Ala Glu Leu Gln Leu Asp Glu Asp Gly Phe Val Glu Ala Thr Glu Gly

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Asp His Ile Leu Ala Gly Ser Phe Glu Thr Ala Met Arg Leu Leu His
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Asp Gln Val Gly Val Ile Gln Phe Gly Pro Tyr Lys Gln Leu Phe Leu
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Gln Thr Tyr Ala Arg Gly Arg Thr Thr Tyr Gln Ala Leu Pro Cys Leu
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Pro Ser Met Tyr Gly Tyr Pro Asn Arg Asn Trp Lys Asp Ala Gly Leu
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Lys Asn Gly Val Pro Ala Val Gly Leu Lys Leu Asn Asp Leu Ile Gln
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Cys Arg Glu Tyr Ile Val Gly Leu Ser Val Glu Thr Glu Arg Lys Lys
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Leu Pro Lys Glu Thr Leu Glu Gln Gln Lys Arg Ile Cys Glu Met Ala
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Thr Asp Ala Tyr Gln Leu Asn Tyr Asp Met His Asn Pro Phe Asp Ile
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Cys Ala Ala Ser Tyr Arg Pro Ile Tyr Arg Gly Lys Pro Val Glu Lys
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Cys Pro Leu Ser Gly Ala Cys Tyr Ser Pro Glu Phe Lys Gly Gln Ile
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<212> DNA
<213> Homo sapiens

<400> 43

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<210> 46
<211> 349
<212> PRT
<213> Homo sapiens

<400> 46

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Cys Arg Cys Pro Asp Glu Pro Ala Pro Arg Cys Pro Ala Gly Val Ser
        35                  40                  45
Leu Val Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu
    50                  55                  60
Gly Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu
65                  70                  75                  80
Phe Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr
                85                  90                  95
Ala Lys Asp Gly Ala Pro Cys Ile Phe Gly Gly Thr Val Tyr Arg Ser
            100                 105                 110
Gly Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp
        115                 120                 125
Gly Ala Val Gly Cys Met Pro Leu Cys Ser Met Asp Val Arg Leu Pro
    130                 135                 140
Ser Pro Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys
145                 150                 155                 160
Cys Glu Glu Trp Val Cys Asp Glu Pro Lys Asp Gln Thr Val Val Gly
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Pro Ala Leu Ala Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro
            180                 185                 190
Thr Met Ile Arg Ala Asn Cys Leu Val Gln Thr Thr Glu Trp Ser Ala
        195                 200                 205
Cys Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp
    210                 215                 220
Asn Ala Ser Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg
225                 230                 235                 240
Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys
                245                 250                 255
Ile Arg Thr Pro Lys Ile Ser Lys Pro Ile Lys Phe Glu Leu Ser Gly
            260                 265                 270
Cys Thr Ser Met Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr
        275                 280                 285
Asp Gly Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu
    290                 295                 300
Phe Lys Cys Pro Asp Gly Glu Val Met Lys Lys Asn Met Met Phe Ile
305                 310                 315                 320
Lys Thr Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe
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Glu Ser Leu Tyr Tyr Arg Lys Met Tyr Gly Asp Met Ala
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<210> 47
<211> 3025
<212> DNA
<213> Homo sapiens

<400> 47
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<210> 48

<211> 752
<212> PRT
<213> Homo sapiens

<400> 48
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Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala
35 40 45
Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln
50 55 60
Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn
65 70 75 80
Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile Asp Glu
85 90 95
Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu Leu Gln
100 105 110
Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala Gly Ile
115 120 125
Met Ala Glu Val Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp
130 135 140
Leu Asn Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys
145 150 155 160
Leu Glu Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu
165 170 175
Glu Asp Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys
180 185 190
Asn Leu Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu
195 200 205
Glu Ser Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg
210 215 220
Leu Glu Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys
225 230 235 240
Thr Leu Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys
245 250 255
Leu Lys Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln
260 265 270
Val Glu Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu
275 280 285
Thr Lys Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr
290 295 300
Ser Val Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu
305 310 315 320
Glu Glu Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn
325 330 335
Arg Leu Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys
340 345 350
Leu Asn Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn
355 360 365
Asn Lys Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys
370 375 380
Leu Lys Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp
385 390 395 400
Glu Tyr Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala
405 410 415
Gln Phe Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys
420 425 430

Tyr Lys Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe
435 440 445
Lys Arg Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu
450 455 460
Val Asp Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp
465 470 475 480
Leu Ile Cys His Leu Gln Gly Asp His Ser Val Cys Lys Lys Lys Leu
485 490 495
Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn
500 505 510
Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg
515 520 525
Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys
530 535 540
Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser
545 550 555 560
Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu
565 570 575
Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser
580 585 590
Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp
595 600 605
Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met
610 615 620
Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu
625 630 635 640
Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His
645 650 655
Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser
660 665 670
Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro
675 680 685
Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys
690 695 700
Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser
705 710 715 720
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725 730 735
Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Leu Phe Arg Phe Trp Leu
740 745 750

<210> 49
<211> 1480
<212> DNA
<213> Homo sapiens

<400> 49
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<210> 50
<211> 205
<212> PRT
<213> Homo sapiens

<400> 50
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Arg Asn Glu Asp Tyr Thr Ile His Val Gln Leu Asn Asp Tyr Val Asp
35 40 45
Ile Ile Cys Pro His Tyr Glu Asp His Ser Val Ala Asp Ala Ala Met
50 55 60
Glu Gln Tyr Ile Leu Tyr Leu Val Glu His Glu Glu Tyr Gln Leu Cys
65 70 75 80
Gln Pro Gln Ser Lys Asp Gln Val Arg Trp Gln Cys Asn Arg Pro Ser
85 90 95
Ala Lys His Gly Pro Glu Lys Leu Ser Glu Lys Phe Gln Arg Phe Thr
100 105 110
Pro Phe Thr Leu Gly Lys Glu Phe Lys Glu Gly His Ser Tyr Tyr Tyr
115 120 125
Ile Ser Lys Pro Ile His Gln His Glu Asp Arg Cys Leu Arg Leu Lys
130 135 140
Val Thr Val Ser Gly Lys Ile Thr His Ser Pro Gln Ala His Val Asn
145 150 155 160
Pro Gln Glu Lys Arg Leu Ala Ala Asp Asp Pro Glu Val Arg Val Leu
165 170 175
His Ser Ile Gly His Ser Ala Ala Pro Arg Leu Phe Pro Leu Ala Trp
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Thr Val Leu Leu Leu Pro Leu Leu Leu Leu Gln Thr Pro
195 200 205

<210> 51
<211> 15952
<212> DNA
<213> Homo sapiens

<400> 51
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Glu His Gly Ile Arg Leu Leu Glu Ala Gln Ile Ala Thr Gly Gly Val
    690                 695                 700
Ile Asp Pro Val His Ser His Arg Val Pro Val Asp Val Ala Tyr Arg
705                 710                 715                 720
Arg Gly Tyr Phe Asp Gln Met Leu Asn Leu Ile Leu Leu Asp Pro Ser
                725                 730                 735
Asp Asp Thr Lys Gly Phe Phe Asp Pro Asn Thr His Glu Asn Leu Thr
            740                 745                 750
Tyr Leu Gln Leu Leu Glu Arg Cys Val Arg Asp Pro Glu Thr Gly Leu
        755                 760                 765
Tyr Leu Leu Pro Leu Ser Ser Thr Gln Ser Pro Leu Val Asp Ser Ala
    770                 775                 780
Thr Gln Gln Ala Phe Gln Asn Leu Leu Leu Ser Val Lys Tyr Gly Arg
785                 790                 795                 800
Phe Gln Gly Gln Arg Val Ser Ala Trp Glu Leu Ile Asn Ser Glu Tyr
                805                 810                 815
Phe Ser Glu Gly Arg Arg Arg Gln Leu Leu Arg Arg Tyr Arg Gln Arg
            820                 825                 830
Glu Val Thr Leu Gly Gln Val Ala Lys Leu Leu Glu Ala Glu Thr Gln
        835                 840                 845
Arg Gln Ala Asp Ile Met Leu Pro Ala Leu Arg Ser Arg Val Thr Val
    850                 855                 860
His Gln Leu Leu Glu Ala Gly Ile Ile Asp Gln Gln Leu Leu Asp Gln
865                 870                 875                 880
Val Leu Ala Gly Thr Ile Ser Pro Glu Ala Leu Leu Leu Met Asp Gly
                885                 890                 895
Val Arg Arg Tyr Leu Cys Gly Leu Gly Ala Val Gly Gly Val Arg Leu
            900                 905                 910
Leu Pro Ser Gly Gln Arg Leu Ser Leu Tyr Gln Ala Met Arg Gln Lys
        915                 920                 925
Leu Leu Gly Pro Arg Val Ala Leu Ala Leu Leu Glu Ala Gln Ala Ala
    930                 935                 940
Thr Gly Thr Ile Met Asp Pro His Ser Pro Glu Ser Leu Ser Val Asp
945                 950                 955                 960
Glu Ala Val Arg Arg Gly Val Val Gly Pro Glu Leu Tyr Gly Arg Leu
                965                 970                 975
Lys Arg Ala Glu Gly Ala Ile Ala Gly Phe Arg Asp Pro Phe Ser Gly
            980                 985                 990
Lys Gln Val Ser Val Phe Gln Ala Met Lys Lys Gly Leu Ile Pro Trp
        995                 1000                1005
Glu Gln Ala Ala Arg Leu Leu Glu Ala Gln Val Ala Thr Gly Gly Ile
    1010                1015                1020
Ile Asp Pro Thr Ser His His His Leu Pro Met Pro Val Ala Ile Gln
1025                1030                1035                1040
Arg Gly Tyr Val Asp Gln Glu Met Glu Thr Ala Leu Ser Ser Ser Ser
                1045                1050                1055
Glu Thr Phe Pro Thr Pro Asp Gly Gln Gly Arg Thr Ser Tyr Ala Gln
            1060                1065                1070
Leu Leu Glu Glu Cys Pro Arg Asp Glu Thr Ser Gly Leu His Leu Leu
        1075                1080                1085
Pro Leu Pro Glu Ser Ala Pro Ala Leu Pro Thr Glu Glu Gln Val Gln
    1090                1095                1100
Arg Ser Leu Gln Ala Val Pro Gly Ala Lys Asp Gly Thr Ser Leu Trp
1105                1110                1115                1120
Asp Leu Leu Ser Ser Cys His Phe Thr Glu Glu Gln Arg Arg Gly Leu
                1125                1130                1135
Leu Glu Asp Val Gln Glu Gly Arg Thr Thr Val Pro Gln Leu Leu Ala
            1140                1145                1150
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Ser Val Gln Arg Trp Val Gln Glu Thr Lys Leu Leu Ala Gln Ala Arg
1155 1160 1165
Val Met Val Pro Gly Pro Arg Gly Glu Val Pro Ala Val Trp Leu Leu
1170 1175 1180
Asp Ala Gly Ile Ile Thr Gln Glu Thr Leu Glu Ala Leu Ala Gln Gly
1185 1190 1195 1200
Thr Gln Ser Pro Ala Gln Val Ala Glu Gln Pro Ala Val Lys Ala Cys
1205 1210 1215
Leu Trp Gly Thr Gly Cys Val Ala Gly Val Leu Leu Gln Pro Ser Gly
1220 1225 1230
Ala Lys Ala Ser Ile Ala Gln Ala Val Arg Asp Gly Leu Leu Pro Thr
1235 1240 1245
Gly Leu Gly Gln Arg Leu Leu Glu Ala Gln Val Ala Ser Gly Phe Leu
1250 1255 1260
Val Asp Pro Leu Asn Asn Gln Arg Leu Ser Val Glu Asp Ala Val Lys
1265 1270 1275 1280
Val Gly Leu Val Gly Arg Glu Leu Ser Glu Gln Leu Gly Gln Ala Glu
1285 1290 1295
Arg Ala Ala Ala Gly Tyr Pro Asp Pro Tyr Ser Arg Ala Ser Leu Ser
1300 1305 1310
Leu Trp Gln Ala Met Glu Lys Gly Leu Val Pro Gln Asn Glu Gly Leu
1315 1320 1325
Pro Leu Leu Gln Val Gln Leu Ala Thr Gly Gly Val Val Asp Pro Val
1330 1335 1340
His Gly Val His Leu Pro Gln Ala Ala Ala Cys Arg Leu Gly Leu Leu
1345 1350 1355 1360
Asp Thr Gln Thr Ser Gln Val Leu Thr Ala Val Asp Lys Asp Asn Lys
1365 1370 1375
Phe Phe Phe Asp Pro Ser Ala Arg Asp Gln Val Thr Tyr Gln Gln Leu
1380 1385 1390
Arg Glu Arg Cys Val Cys Asp Ser Glu Thr Gly Leu Leu Leu Leu Pro
1395 1400 1405
Leu Pro Ser Asp Thr Val Leu Glu Val Asp Asp His Thr Ala Val Ala
1410 1415 1420
Leu Arg Ala Met Lys Val Pro Val Ser Thr Gly Arg Phe Lys Gly Cys
1425 1430 1435 1440
Ser Val Ser Leu Trp Asp Leu Leu Leu Ser Glu Tyr Val Gly Ala Asp
1445 1450 1455
Lys Arg Arg Glu Leu Val Ala Leu Cys Arg Ser Gly Arg Ala Ala Ala
1460 1465 1470
Leu Arg Gln Val Val Ser Ala Val Thr Ala Leu Val Glu Ala Ala Glu
1475 1480 1485
Arg Gln Pro Leu Gln Ala Thr Phe Arg Gly Leu Arg Lys Gln Val Ser
1490 1495 1500
Ala Arg Asp Leu Phe Arg Ala Gln Leu Ile Ser Arg Lys Thr Leu Asp
1505 1510 1515 1520
Glu Leu Ser Gln Gly Thr Thr Thr Val Lys Glu Val Ala Glu Met Asp
1525 1530 1535
Ser Val Lys Arg Ser Leu Glu Gly Gly Asn Phe Ile Ala Gly Val Leu
1540 1545 1550
Ile Gln Gly Thr Gln Glu Arg Met Ser Ile Pro Glu Ala Leu Arg Arg
1555 1560 1565
His Ile Leu Arg Pro Gly Thr Ala Leu Val Leu Leu Glu Ala Gln Ala
1570 1575 1580
Ala Thr Gly Phe Ile Ile Asp Pro Ala Glu Asn Arg Lys Leu Thr Val
1585 1590 1595 1600
Glu Glu Ala Phe Lys Ala Gly Met Phe Gly Lys Glu Thr Tyr Val Lys
1605 1610 1615
Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Thr Asp Pro Tyr Thr

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            1620                1625                1630
Gly Gln Gln Ile Ser Leu Phe Gln Ala Met Gln Lys Asp Leu Ile Val
        1635                1640                1645
Arg Glu His Gly Ile Arg Leu Leu Glu Ala Gln Ile Ala Thr Gly Gly
    1650                1655                1660
Ile Ile Asp Pro Val His Ser His Arg Val Pro Val Asp Val Ala Tyr
1665                1670                1675                1680
Arg Cys Gly Tyr Phe Asp Glu Glu Met Asn Arg Ile Leu Ala Asp Pro
                1685                1690                1695
Ser Asp Asp Thr Lys Gly Phe Phe Asp Pro Asn Thr His Glu Asn Leu
            1700                1705                1710
Thr Tyr Leu Gln Leu Leu Glu Arg Cys Val Glu Asp Pro Glu Thr Gly
        1715                1720                1725
Leu Tyr Leu Leu Gln Ile Ile Lys Lys Gly Glu Asn Tyr Val Tyr Ile
    1730                1735                1740
Asn Glu Ala Thr Arg His Val Leu Gln Ser Arg Thr Ala Lys Met Arg
1745                1750                1755                1760
Val Gly Arg Phe Ala Asp Gln Val Val Ser Phe Trp Asp Leu Leu Ser
                1765                1770                1775
Ser Pro Tyr Phe Thr Glu Asp Arg Lys Arg Glu Leu Ile Gln Glu Tyr
            1780                1785                1790
Gly Ala Gln Ser Gly Gly Leu Glu Lys Leu Leu Glu Ile Ile Thr Thr
        1795                1800                1805
Thr Ile Glu Glu Thr Glu Thr Gln Asn Gln Gly Ile Lys Val Ala Ala
    1810                1815                1820
Ile Arg Gly Glu Val Thr Ala Ala Asp Leu Phe Asn Ser Arg Val Ile
1825                1830                1835                1840
Asp Gln Lys Thr Leu His Thr Leu Arg Val Gly Arg Thr Gly Gly Gln
                1845                1850                1855
Ala Leu Ser Thr Leu Glu Cys Val Lys Pro Tyr Leu Glu Gly Ser Asp
            1860                1865                1870
Cys Ile Ala Gly Val Thr Val Pro Ser Thr Arg Glu Val Met Ser Leu
        1875                1880                1885
His Glu Ala Ser Arg Lys Glu Leu Ile Pro Ala Ala Phe Ala Thr Trp
    1890                1895                1900
Leu Leu Glu Ala Gln Ala Ala Thr Gly Phe Leu Leu Asp Pro Cys Thr
1905                1910                1915                1920
Arg Gln Lys Leu Ser Val Asp Glu Ala Val Asp Val Gly Leu Val Asn
                1925                1930                1935
Glu Glu Leu Arg Glu Arg Leu Leu Lys Ala Glu Arg Ala Ala Thr Gly
            1940                1945                1950
Tyr Arg Asp Pro Ala Thr Gly Asp Thr Ile Pro Leu Phe Gln Ala Met
        1955                1960                1965
Gln Lys Gln Leu Ile Glu Lys Ala Glu Ala Leu Arg Leu Leu Glu Val
    1970                1975                1980
Gln Val Ala Thr Gly Gly Val Ile Asp Pro Gln His His His Arg Leu
1985                1990                1995                2000
Pro Leu Glu Thr Ala Tyr Arg Arg Gly Cys Leu His Lys Asp Ile Tyr
                2005                2010                2015
Ala Leu Ile Ser Asp Gln Lys His Met Arg Lys Arg Phe Val Asp Pro
            2020                2025                2030
Asn Thr Gln Glu Lys Val Ser Tyr Arg Glu Leu Gln Glu Arg Cys Arg
        2035                2040                2045
Pro Gln Glu Asp Thr Gly Trp Val Leu Phe Pro Val Asn Lys Ala Ala
    2050                2055                2060
Arg Asp Ser Glu His Ile Asp Asp Glu Thr Arg Arg Ala Leu Glu Ala
2065                2070                2075                2080
Glu Gln Val Glu Ile Thr Val Gly Arg Phe Arg Gly Gln Lys Pro Thr
                2085                2090                2095
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Leu Trp Ala Leu Leu Asn Ser Glu Tyr Val Thr Glu Glu Lys Lys Leu
2100 2105 2110
Gln Leu Val Arg Met Tyr Arg Thr His Thr Arg Arg Ala Leu Gln Thr
2115 2120 2125
Val Ala Gln Leu Ile Leu Glu Leu Ile Glu Lys Gln Glu Thr Ser Asn
2130 2135 2140
Lys His Leu Trp Phe Gln Gly Ile Arg Arg Gln Ile Thr Ala Ser Glu
2145 2150 2155 2160
Leu Leu Ser Ser Ala Ile Ile Thr Glu Glu Met Leu Gln Asp Leu Glu
2165 2170 2175
Thr Gly Arg Ser Thr Thr Gln Glu Leu Met Glu Asp Asp Arg Val Lys
2180 2185 2190
Arg Tyr Leu Glu Gly Thr Ser Cys Ile Ala Gly Val Leu Val Pro Ala
2195 2200 2205
Lys Asp Gln Pro Gly Arg Gln Glu Lys Met Ser Ile Tyr Gln Ala Met
2210 2215 2220
Trp Lys Gly Val Leu Arg Pro Gly Thr Ala Leu Val Leu Leu Glu Ala
2225 2230 2235 2240
Gln Ala Ala Thr Gly Phe Val Ile Asp Pro Val Arg Asn Leu Arg Leu
2245 2250 2255
Ser Val Glu Glu Pro Val Pro Ala Gly Val Val Gly Ser Glu Ile Gln
2260 2265 2270
Glu Lys Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Thr Asp Pro
2275 2280 2285
Tyr Thr Gly Gln Gln Ile Ser Leu Phe Gln Ala Met Gln Lys Asp Leu
2290 2295 2300
Ile Val Arg Glu His Gly Ile Arg Leu Leu Glu Ala Gln Ile Ala Thr
2305 2310 2315 2320
Gly Gly Val Ile Asp Pro Val His Ser His Arg Val Pro Val Asp Val
2325 2330 2335
Ala Tyr Arg Arg Gly Tyr Phe Asp Glu Glu Met Asn Arg Val Leu Ala
2340 2345 2350
Asp Pro Ser Asp Asp Thr Lys Gly Phe Phe Asp Pro Asn Thr His Glu
2355 2360 2365
Asn Leu Thr Tyr Val Gln Leu Leu Arg Arg Cys Val Pro Asp Pro Asp
2370 2375 2380
Thr Gly Leu Tyr Met Leu Gln Leu Ala Gly Arg Gly Ser Ala Val His
2385 2390 2395 2400
Gln Leu Ser Glu Glu Leu Arg Cys Ala Leu Arg Asp Ala Arg Val Thr
2405 2410 2415
Pro Gly Ser Gly Ala Leu Gln Gly Gln Ser Val Ser Val Trp Glu Leu
2420 2425 2430
Leu Phe Tyr Arg Glu Val Ser Glu Asp Arg Arg Gln Asp Leu Leu Ser
2435 2440 2445
Arg Tyr Arg Ala Gly Thr Leu Thr Val Glu Glu Leu Gly Ala Thr Leu
2450 2455 2460
Thr Ser Leu Leu Ala Gln Ala Gln Ala Gln Ala Arg Ala Glu Ala Glu
2465 2470 2475 2480
Ala Gly Ser Pro Arg Pro Asp Pro Arg Glu Ala Leu Arg Ala Ala Thr
2485 2490 2495
Met Glu Val Lys Val Gly Arg Leu Arg Gly Arg Ala Val Pro Val Trp
2500 2505 2510
Asp Val Leu Ala Ser Gly Tyr Val Ser Arg Ala Ala Arg Glu Glu Leu
2515 2520 2525
Leu Ala Glu Phe Gly Ser Gly Thr Leu Asp Leu Pro Ala Leu Thr Arg
2530 2535 2540
Arg Leu Thr Ala Ile Ile Glu Glu Ala Glu Glu Ala Pro Gly Ala Arg
2545 2550 2555 2560
Pro Gln Leu Gln Asp Ala Arg Arg Gly Pro Arg Glu Pro Gly Pro Ala

2565 2570 2575
Gly Arg Gly Asp Gly Asp Ser Gly Arg Ser Gln Arg Glu Gly Gln Gly
2580 2585 2590
Glu Gly Glu Thr Gln Glu Ala Ala Ala Ala Ala Ala Ala Ala Arg Arg
2595 2600 2605
Gln Glu Gln Thr Leu Arg Asp Ala Thr Met Glu Val Gln Arg Gly Gln
2610 2615 2620
Phe Gln Gly Arg Pro Val Ser Val Trp Asp Val Leu Phe Ser Ser Tyr
2625 2630 2635 2640
Leu Ser Glu Ala Arg Arg Asp Glu Leu Leu Ala Gln His Ala Ala Gly
2645 2650 2655
Ala Leu Gly Leu Pro Asp Leu Val Ala Val Leu Thr Arg Val Ile Glu
2660 2665 2670
Glu Thr Glu Glu Arg Leu Ser Lys Val Ser Phe Arg Gly Leu Arg Arg
2675 2680 2685
Gln Val Ser Ala Ser Glu Leu His Thr Ser Gly Ile Leu Gly Pro Glu
2690 2695 2700
Thr Leu Arg Asp Leu Ala Gln Gly Thr Lys Thr Leu Gln Glu Val Thr
2705 2710 2715 2720
Glu Met Asp Ser Val Lys Arg Tyr Leu Glu Gly Thr Ser Cys Ile Ala
2725 2730 2735
Gly Val Leu Val Pro Ala Lys Asp Gln Pro Gly Arg Gln Glu Lys Met
2740 2745 2750
Ser Ile Tyr Gln Ala Met Trp Lys Gly Val Leu Arg Pro Gly Thr Ala
2755 2760 2765
Leu Val Leu Leu Glu Ala Gln Ala Ala Thr Gly Phe Val Ile Asp Pro
2770 2775 2780
Val Arg Asn Leu Arg Leu Ser Val Glu Glu Ala Val Ala Ala Gly Val
2785 2790 2795 2800
Val Gly Gly Glu Ile Gln Glu Lys Leu Leu Ser Ala Glu Arg Ala Val
2805 2810 2815
Thr Gly Tyr Thr Asp Pro Tyr Thr Gly Gln Gln Ile Ser Leu Phe Gln
2820 2825 2830
Ala Met Gln Lys Asp Leu Ile Val Arg Glu His Gly Ile Arg Leu Leu
2835 2840 2845
Glu Ala Gln Ile Ala Thr Gly Gly Val Ile Asp Pro Val His Ser His
2850 2855 2860
Arg Val Pro Val Asp Val Ala Tyr Arg Arg Gly Tyr Phe Asp Glu Glu
2865 2870 2875 2880
Met Asn Arg Val Leu Ala Asp Pro Ser Asp Asp Thr Lys Gly Phe Phe
2885 2890 2895
Asp Pro Asn Thr His Glu Asn Leu Thr Tyr Val Gln Leu Leu Arg Arg
2900 2905 2910
Cys Val Pro Asp Pro Asp Thr Gly Leu Tyr Met Leu Gln Leu Ala Gly
2915 2920 2925
Arg Gly Ser Ala Val His Gln Leu Ser Glu Glu Leu Arg Cys Ala Leu
2930 2935 2940
Arg Asp Ala Arg Val Thr Pro Gly Ser Gly Ala Leu Gln Gly Gln Ser
2945 2950 2955 2960
Val Ser Val Trp Glu Leu Leu Phe Tyr Arg Glu Val Ser Glu Asp Arg
2965 2970 2975
Arg Gln Asp Leu Leu Ser Arg Tyr Arg Ala Gly Thr Leu Thr Val Glu
2980 2985 2990
Glu Leu Gly Ala Thr Leu Thr Ser Leu Leu Ala Gln Ala Gln Ala Gln
2995 3000 3005
Ala Arg Ala Glu Ala Glu Ala Gly Ser Pro Arg Pro Asp Pro Arg Glu
3010 3015 3020
Ala Leu Arg Ala Ala Thr Met Glu Val Lys Val Gly Arg Leu Arg Gly
3025 3030 3035 3040

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Arg Ala Val Pro Val Trp Asp Val Leu Ala Ser Gly Tyr Val Ser Gly
                3045                3050                3055
Ala Ala Arg Glu Glu Leu Leu Ala Glu Phe Gly Ser Gly Thr Leu Asp
            3060                3065                3070
Leu Pro Ala Leu Thr Arg Arg Leu Thr Ala Ile Ile Glu Glu Ala Glu
        3075                3080                3085
Glu Ala Pro Gly Ala Arg Pro Gln Leu Gln Asp Ala Trp Arg Gly Pro
    3090                3095                3100
Arg Glu Pro Gly Pro Ala Gly Arg Gly Asp Gly Asp Ser Gly Arg Ser
3105                3110                3115                3120
Gln Arg Glu Gly Gln Gly Glu Gly Glu Thr Gln Glu Ala Ala Ala Ala
                3125                3130                3135
Ala Ala Ala Ala Arg Arg Gln Glu Gln Thr Leu Arg Asp Ala Thr Met
            3140                3145                3150
Glu Val Gln Arg Gly Gln Phe Gln Gly Arg Pro Val Ser Val Trp Asp
        3155                3160                3165
Val Leu Phe Ser Ser Tyr Leu Ser Glu Ala Arg Arg Asp Glu Leu Leu
    3170                3175                3180
Ala Gln His Ala Ala Gly Ala Leu Gly Leu Pro Asp Leu Val Ala Val
3185                3190                3195                3200
Leu Thr Arg Val Ile Glu Glu Thr Glu Glu Arg Leu Ser Lys Val Ser
                3205                3210                3215
Phe Arg Gly Leu Arg Arg Gln Val Ser Ala Ser Glu Leu His Thr Ser
            3220                3225                3230
Gly Ile Leu Gly Pro Glu Thr Leu Arg Asp Leu Ala Gln Gly Thr Lys
        3235                3240                3245
Thr Leu Gln Glu Val Thr Glu Met Asp Ser Val Lys Arg Tyr Leu Glu
    3250                3255                3260
Gly Thr Ser Cys Ile Ala Gly Val Leu Val Pro Ala Lys Asp Gln Pro
3265                3270                3275                3280
Gly Arg Gln Glu Lys Met Ser Ile Tyr Gln Ala Met Trp Lys Gly Val
                3285                3290                3295
Leu Arg Pro Gly Thr Ala Leu Val Leu Leu Glu Ala Gln Ala Ala Thr
            3300                3305                3310
Gly Phe Val Ile Asp Pro Val Arg Asn Leu Arg Leu Ser Val Glu Glu
        3315                3320                3325
Ala Val Ala Ala Gly Val Val Gly Gly Glu Ile Gln Glu Lys Leu Leu
    3330                3335                3340
Ser Ala Glu Arg Ala Val Thr Gly Tyr Thr Asp Pro Tyr Thr Gly Gln
3345                3350                3355                3360
Gln Ile Ser Leu Phe Gln Ala Met Gln Lys Asp Leu Ile Val Arg Glu
                3365                3370                3375
His Gly Ile Arg Leu Leu Glu Ala Gln Ile Ala Thr Gly Gly Val Ile
            3380                3385                3390
Asp Pro Val His Ser His Arg Val Pro Val Asp Val Ala Tyr Arg Arg
        3395                3400                3405
Gly Tyr Phe Asp Glu Glu Met Asn Arg Val Leu Ala Asp Pro Ser Asp
    3410                3415                3420
Asp Thr Lys Gly Phe Phe Asp Pro Asn Thr His Glu Asn Leu Thr Tyr
3425                3430                3435                3440
Val Gln Leu Leu Arg Arg Cys Val Pro Asp Pro Asp Thr Gly Leu Tyr
                3445                3450                3455
Met Leu Gln Leu Ala Gly Arg Gly Ser Ala Val His Gln Leu Ser Glu
            3460                3465                3470
Glu Leu Arg Cys Ala Leu Arg Asp Ala Arg Val Thr Pro Gly Ser Gly
        3475                3480                3485
Ala Leu Gln Gly Gln Ser Val Ser Val Trp Glu Leu Leu Phe Tyr Arg
    3490                3495                3500
Glu Val Ser Glu Asp Arg Arg Gln Asp Leu Leu Ser Arg Tyr Arg Ala
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3505 3510 3515 3520
Gly Thr Leu Thr Val Glu Glu Leu Gly Ala Thr Leu Thr Ser Leu Leu
3525 3530 3535
Ala Gln Ala Gln Ala Gln Ala Arg Ala Glu Ala Glu Ala Gly Ser Pro
3540 3545 3550
Arg Pro Asp Pro Arg Glu Ala Leu Arg Ala Ala Thr Met Glu Val Lys
3555 3560 3565
Val Gly Arg Leu Arg Gly Arg Ala Val Pro Val Trp Asp Val Leu Ala
3570 3575 3580
Ser Gly Tyr Val Ser Gly Ala Ala Arg Glu Glu Leu Leu Ala Glu Phe
3585 3590 3595 3600
Gly Ser Gly Thr Leu Asp Leu Pro Ala Leu Thr Arg Arg Leu Thr Ala
3605 3610 3615
Ile Ile Glu Glu Ala Glu Glu Ala Pro Gly Ala Arg Pro Gln Leu Gln
3620 3625 3630
Asp Ala Trp Arg Gly Pro Arg Glu Pro Gly Pro Ala Gly Arg Gly Asp
3635 3640 3645
Gly Asp Ser Gly Arg Ser Gln Arg Glu Gly Gln Gly Glu Gly Glu Thr
3650 3655 3660
Gln Glu Ala Ala Ala Ala Ala Ala Ala Ala Arg Arg Gln Glu Gln Thr
3665 3670 3675 3680
Leu Arg Asp Ala Thr Met Glu Val Gln Arg Gly Gln Phe Gln Gly Arg
3685 3690 3695
Pro Val Ser Val Trp Asp Val Leu Phe Ser Ser Tyr Leu Ser Glu Ala
3700 3705 3710
Arg Arg Asp Glu Leu Leu Ala Gln His Ala Ala Gly Ala Leu Gly Leu
3715 3720 3725
Pro Asp Leu Val Ala Val Leu Thr Arg Val Ile Glu Glu Thr Glu Glu
3730 3735 3740
Arg Leu Ser Lys Val Ser Phe Arg Gly Leu Arg Arg Gln Val Ser Ala
3745 3750 3755 3760
Ser Glu Leu His Thr Ser Gly Ile Leu Gly Pro Glu Thr Leu Arg Asp
3765 3770 3775
Leu Ala Gln Gly Thr Lys Thr Leu Gln Glu Val Thr Glu Met Asp Ser
3780 3785 3790
Val Lys Arg Tyr Leu Glu Gly Thr Ser Cys Ile Ala Gly Val Leu Val
3795 3800 3805
Pro Ala Lys Asp Gln Pro Gly Arg Gln Glu Lys Met Ser Ile Tyr Gln
3810 3815 3820
Ala Met Trp Lys Gly Val Leu Arg Pro Gly Thr Ala Leu Val Leu Leu
3825 3830 3835 3840
Glu Ala Gln Ala Ala Thr Gly Phe Val Ile Asp Pro Val Arg Asn Leu
3845 3850 3855
Arg Leu Ser Val Glu Glu Ala Val Ala Ala Gly Val Val Gly Gly Glu
3860 3865 3870
Ile Gln Glu Lys Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Thr
3875 3880 3885
Asp Pro Tyr Thr Gly Gln Gln Ile Ser Leu Phe Gln Ala Met Gln Lys
3890 3895 3900
Asp Leu Ile Val Arg Glu His Gly Ile Arg Leu Leu Glu Ala Gln Ile
3905 3910 3915 3920
Ala Thr Gly Gly Val Ile Asp Pro Val His Ser His Arg Val Pro Val
3925 3930 3935
Asp Val Ala Tyr Arg Arg Gly Tyr Phe Asp Glu Glu Met Asn Arg Val
3940 3945 3950
Leu Ala Asp Pro Ser Asp Asp Thr Lys Gly Phe Phe Asp Pro Asn Thr
3955 3960 3965
His Glu Asn Leu Thr Tyr Val Gln Leu Leu Arg Arg Cys Val Pro Asp
3970 3975 3980

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Pro Asp Thr Gly Leu Tyr Met Leu Gln Leu Ala Gly Arg Gly Ser Ala
3985                3990                3995                4000
Val His Gln Leu Ser Glu Glu Leu Arg Cys Ala Leu Arg Asp Ala Arg
                4005                4010                4015
Val Thr Pro Gly Ser Gly Ala Leu Gln Gly Gln Ser Val Ser Val Trp
            4020                4025                4030
Glu Leu Leu Phe Tyr Arg Glu Val Ser Glu Asp Arg Arg Gln Asp Leu
        4035                4040                4045
Leu Ser Arg Tyr Arg Ala Ser Thr Leu Thr Val Glu Glu Leu Gly Ala
    4050                4055                4060
Thr Leu Thr Ser Leu Leu Ala Gln Ala Gln Ala Gln Ala Arg Ala Glu
4065                4070                4075                4080
Ala Glu Ala Gly Ser Pro Arg Pro Asp Pro Arg Glu Ala Leu Arg Ala
                4085                4090                4095
Ala Thr Met Glu Val Lys Val Gly Arg Leu Arg Gly Arg Ala Val Pro
            4100                4105                4110
Val Trp Asp Val Leu Ala Ser Gly Tyr Val Ser Arg Ala Ala Arg Glu
        4115                4120                4125
Glu Leu Leu Ala Glu Phe Gly Ser Gly Thr Leu Asp Leu Pro Ala Leu
    4130                4135                4140
Thr Arg Arg Leu Thr Ala Ile Ile Glu Glu Ala Glu Glu Ala Pro Gly
4145                4150                4155                4160
Ala Arg Pro Gln Leu Gln Asp Ala Trp Arg Gly Pro Arg Glu Pro Gly
                4165                4170                4175
Pro Ala Gly Arg Gly Asp Gly Asp Ser Gly Arg Ser Gln Arg Glu Gly
            4180                4185                4190
Gln Gly Glu Gly Glu Thr Gln Glu Ala Ala Ala Ala Thr Ala Ala Ala
        4195                4200                4205
Arg Arg Gln Glu Gln Thr Leu Arg Asp Ala Thr Met Glu Val Gln Arg
    4210                4215                4220
Gly Gln Phe Gln Gly Arg Pro Val Ser Val Trp Asp Val Leu Phe Ser
4225                4230                4235                4240
Ser Tyr Leu Ser Glu Ala Arg Arg Asp Glu Leu Leu Ala Gln His Ala
                4245                4250                4255
Ala Gly Ala Leu Gly Leu Pro Asp Leu Val Ala Val Leu Thr Arg Val
            4260                4265                4270
Ile Glu Glu Thr Glu Glu Arg Leu Ser Lys Val Ser Phe Arg Gly Leu
        4275                4280                4285
Arg Arg Gln Val Ser Ala Ser Glu Leu His Thr Ser Gly Ile Leu Gly
    4290                4295                4300
Pro Glu Thr Leu Arg Asp Leu Ala Gln Gly Thr Lys Thr Leu Gln Glu
4305                4310                4315                4320
Val Thr Glu Met Asp Ser Val Lys Arg Tyr Leu Glu Gly Thr Ser Cys
                4325                4330                4335
Ile Ala Gly Val Leu Val Pro Ala Lys Asp Gln Pro Gly Arg Gln Glu
            4340                4345                4350
Lys Met Ser Ile Tyr Gln Ala Met Trp Lys Gly Val Leu Arg Pro Gly
        4355                4360                4365
Thr Ala Leu Val Leu Leu Glu Ala Gln Ala Ala Thr Gly Phe Val Ile
    4370                4375                4380
Asp Pro Val Arg Asn Leu Arg Leu Ser Val Glu Glu Ala Val Ala Ala
4385                4390                4395                4400
Gly Val Val Gly Gly Glu Ile Gln Glu Lys Leu Leu Ser Ala Glu Arg
                4405                4410                4415
Ala Val Thr Gly Tyr Thr Asp Pro Tyr Thr Gly Gln Gln Ile Ser Leu
            4420                4425                4430
Phe Gln Ala Met Gln Lys Asp Leu Ile Val Arg Glu His Gly Ile Arg
        4435                4440                4445
Leu Leu Glu Ala Gln Ile Ala Thr Gly Gly Val Ile Asp Pro Val His
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4450 4455 4460
Ser His Arg Val Pro Val Asp Val Ala Tyr Arg Arg Gly Tyr Phe Asp
4465 4470 4475 4480
Glu Glu Met Asn Arg Val Leu Ala Asp Pro Ser Asp Asp Thr Lys Gly
4485 4490 4495
Phe Phe Asp Pro Asn Thr His Glu Asn Leu Thr Tyr Val Gln Leu Leu
4500 4505 4510
Arg Arg Cys Val Pro Asp Pro Asp Thr Gly Leu Tyr Met Leu Gln Leu
4515 4520 4525
Ala Gly Arg Gly Ser Ala Val His Gln Leu Ser Glu Glu Leu Arg Cys
4530 4535 4540
Ala Leu Arg Asp Ala Arg Val Thr Pro Gly Ser Gly Ala Leu Gln Gly
4545 4550 4555 4560
Gln Ser Val Ser Val Trp Glu Leu Leu Phe Tyr Arg Glu Val Ser Glu
4565 4570 4575
Asp Arg Arg Gln Asp Leu Leu Ser Arg Tyr Arg Ala Gly Thr Leu Thr
4580 4585 4590
Val Glu Glu Leu Gly Ala Thr Leu Thr Ser Leu Leu Ala Gln Ala Gln
4595 4600 4605
Ala Gln Ala Arg Ala Glu Ala Glu Ala Gly Ser Pro Arg Pro Asp Pro
4610 4615 4620
Arg Glu Ala Leu Arg Ala Ala Thr Met Glu Val Lys Val Gly Arg Leu
4625 4630 4635 4640
Arg Gly Arg Ala Val Pro Val Trp Asp Val Leu Ala Ser Gly Tyr Val
4645 4650 4655
Ser Gly Ala Ala Arg Glu Glu Leu Leu Ala Glu Phe Gly Ser Gly Thr
4660 4665 4670
Leu Asp Leu Pro Ala Leu Thr Arg Arg Leu Thr Ala Ile Ile Glu Glu
4675 4680 4685
Ala Glu Glu Ala Pro Gly Ala Arg Pro Gln Leu Gln Asp Ala Trp Arg
4690 4695 4700
Gly Pro Arg Glu Pro Gly Pro Ala Gly Arg Gly Asp Gly Asp Ser Gly
4705 4710 4715 4720
Arg Ser Gln Arg Glu Gly Gln Gly Glu Gly Glu Thr Gln Glu Ala Ala
4725 4730 4735
Ala Ala Ala Ala Ala Ala Arg Arg Gln Glu Gln Thr Leu Arg Asp Ala
4740 4745 4750
Thr Met Glu Val Gln Arg Gly Gln Phe Gln Gly Arg Pro Val Ser Val
4755 4760 4765
Trp Asp Val Leu Phe Ser Ser Tyr Leu Ser Glu Ala Arg Arg Asp Glu
4770 4775 4780
Leu Leu Ala Gln His Ala Ala Gly Ala Leu Gly Leu Pro Asp Leu Val
4785 4790 4795 4800
Ala Val Leu Thr Arg Val Ile Glu Glu Thr Glu Glu Arg Leu Ser Lys
4805 4810 4815
Val Ser Phe Arg Gly Leu Arg Arg Gln Val Ser Ala Ser Glu Leu His
4820 4825 4830
Thr Ser Gly Ile Leu Gly Pro Glu Thr Leu Arg Asp Leu Ala Gln Gly
4835 4840 4845
Thr Lys Thr Leu Gln Glu Val Thr Glu Met Asp Ser Val Lys Arg Tyr
4850 4855 4860
Leu Glu Gly Thr Ser Cys Ile Ala Gly Val Leu Val Pro Ala Lys Asp
4865 4870 4875 4880
Gln Pro Gly Arg Gln Glu Lys Met Ser Ile Tyr Gln Ala Met Trp Lys
4885 4890 4895
Gly Val Leu Arg Pro Gly Thr Ala Leu Val Leu Leu Glu Ala Gln Ala
4900 4905 4910
Ala Thr Gly Phe Val Ile Asp Pro Val Arg Asn Leu Arg Leu Ser Val
4915 4920 4925

Glu Glu Ala Val Ala Ala Gly Val Val Gly Gly Glu Ile Gln Glu Lys
    4930   4935   4940
Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Thr Asp Pro Tyr Thr
4945   4950   4955   4960
Gly Gln Gln Ile Ser Leu Phe Gln Ala Met Gln Lys Asp Leu Ile Val
                4965   4970   4975
Arg Glu His Gly Ile Arg Leu Leu Glu Ala Gln Ile Ala Thr Gly Gly
            4980   4985   4990
Val Ile Asp Pro Val His Ser His Arg Val Pro Val Asp Val Ala Tyr
        4995   5000   5005
Arg Arg Gly Tyr Phe Asp Glu Glu Met Asn Arg Val Leu Ala Asp Pro
    5010   5015   5020
Ser Asp Asp Thr Lys Gly Phe Phe Asp Pro Asn Thr His Glu Asn Leu
5025   5030   5035   5040
Thr Tyr Leu Gln Leu Leu Gln Arg Ala Thr Leu Asp Pro Glu Thr Gly
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Leu Leu Phe Leu Ser Leu Ser Leu Gln
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<210> 53
<211> 1664
<212> DNA
<213> Homo sapiens

<400> 53
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gccgggctag gcaattgcag ttaatacata caggggttag tgaagggctt attaagttgt 1620
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<210> 54
<211> 313
<212> PRT
<213> Homo sapiens

<400> 54
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            20   25   30
Thr Glu Phe Pro Glu Leu Ala Pro Ser Gln Asn Gln Asn His Leu Lys
        35   40   45
Asp Trp Phe Leu Glu Asn Lys Ser Glu Val Cys Glu Cys Arg Asn Asn
    50   55   60
Glu Asp Gly Pro Gly Leu Ile Met Glu Glu Gln His Lys Cys Ser Ser
65   70   75   80
Lys Ser Leu Glu His Lys Thr Gln Thr Pro Pro Val Glu Glu Asn Val
                85   90   95
Thr Gln Lys Ile Ser Asp Leu Glu Ile Cys Ala Asp Glu Phe Pro Gly
            100   105   110
Ser Ser Ala Thr Tyr Arg Ile Leu Glu Val Gly Cys Gly Val Gly Asn
        115   120   125
Thr Val Phe Pro Ile Leu Gln Thr Asn Asn Asp Pro Gly Leu Phe Val
    130   135   140
Tyr Cys Cys Asp Phe Ser Ser Thr Ala Ile Glu Leu Val Gln Thr Asn
145   150   155   160
Ser Glu Tyr Asp Pro Ser Arg Cys Phe Ala Phe Val His Asp Leu Cys
                165   170   175
Asp Glu Glu Lys Ser Tyr Pro Val Pro Lys Gly Ser Leu Asp Ile Ile
            180   185   190
Ile Leu Ile Phe Val Leu Ser Ala Ile Val Pro Asp Lys Met Gln Lys
        195   200   205
Ala Ile Asn Arg Leu Ser Arg Leu Leu Lys Pro Gly Gly Met Val Leu
    210   215   220
Leu Arg Asp Tyr Gly Arg Tyr Asp Met Ala Gln Leu Arg Phe Lys Lys
225   230   235   240
Gly Gln Cys Leu Ser Gly Asn Phe Tyr Val Arg Gly Asp Gly Thr Arg
                245   250   255
Val Tyr Phe Phe Thr Gln Glu Glu Leu Asp Thr Leu Phe Thr Thr Ala
            260   265   270
Gly Leu Glu Lys Val Gln Asn Leu Val Asp Arg Arg Leu Gln Val Asn
        275   280   285
Arg Gly Lys Gln Leu Thr Met Tyr Arg Val Trp Ile Gln Cys Lys Tyr
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Cys Lys Pro Leu Leu Ser Ser Thr Ser
305   310

<210> 55
<211> 3334
<212> DNA
<213> Homo sapiens

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tctaagattt ggagctgcag gaaaagaatt acagttgagt acctccagca cattgtggaa 240
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tcagatgggt tgaggcagct gcttcacaac aggatcacag tctttctgtc cacatggaac 480
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tgtttgtaca gaaatatact ggcctagcag aggc 3334

<210> 56
<211> 509
<212> PRT
<213> Homo sapiens

<400> 56
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Ala Lys Ile Ile Tyr Gly Asp Pro Val Thr Phe Leu Pro His Leu Pro
20 25 30
Arg Lys Ser Val Val His Cys Ser Lys Ile Trp Ser Cys Arg Lys Arg

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        35                  40                  45
Ile Thr Val Glu Tyr Leu Gln His Ile Val Glu Gln Lys Asn Gly Lys
    50                  55                  60
Glu Arg Val Pro Ile Leu Trp His Phe Leu Gln Lys Glu Ala Glu Leu
65                  70                  75                  80
Arg Leu Val Lys Phe Leu Pro Glu Ile Leu Ala Leu Gln Arg Asp Leu
                85                  90                  95
Val Lys Gln Phe Gln Asn Val Gln Gln Val Glu Tyr Ser Ser Ile Arg
            100                 105                 110
Gly Phe Leu Ser Lys His Ser Ser Asp Gly Leu Arg Gln Leu Leu His
        115                 120                 125
Asn Arg Ile Thr Val Phe Leu Ser Thr Trp Asn Lys Leu Arg Arg Ser
    130                 135                 140
Leu Glu Thr Asn Gly Glu Ile Asn Leu Pro Lys Asp Tyr Cys Ser Thr
145                 150                 155                 160
Asp Leu Asp Leu Asp Thr Glu Phe Glu Ile Leu Leu Pro Arg Arg Arg
                165                 170                 175
Gly Leu Gly Leu Cys Ala Thr Ala Leu Val Ser Tyr Leu Ile Arg Leu
            180                 185                 190
His Asn Glu Ile Val Tyr Ala Val Glu Lys Leu Ser Lys Glu Asn Asn
        195                 200                 205
Ser Tyr Ser Val Asp Ala Ala Glu Val Thr Glu Leu His Val Ile Ser
    210                 215                 220
Tyr Glu Val Glu Arg Asp Leu Thr Pro Leu Ile Leu Ser Asn Cys Gln
225                 230                 235                 240
Tyr Gln Val Glu Glu Gly Arg Glu Thr Val Gln Glu Phe Asp Leu Glu
                245                 250                 255
Lys Ile Gln Arg Gln Ile Val Ser Arg Phe Leu Gln Gly Lys Pro Arg
            260                 265                 270
Leu Ser Leu Lys Gly Ile Pro Thr Leu Val Tyr Arg His Asp Trp Asn
        275                 280                 285
Tyr Glu His Leu Phe Met Asp Ile Lys Asn Lys Met Ala Gln Asp Ser
    290                 295                 300
Leu Pro Ser Ser Val Ile Ser Ala Ile Ser Gly Gln Leu Gln Ser Tyr
305                 310                 315                 320
Ser Asp Ala Cys Glu Val Leu Ser Val Val Glu Val Thr Leu Gly Phe
                325                 330                 335
Leu Ser Thr Ala Gly Gly Asp Pro Asn Met Gln Leu Asn Val Tyr Thr
            340                 345                 350
Gln Asp Ile Leu Gln Met Gly Asp Gln Thr Ile His Val Leu Lys Ala
        355                 360                 365
Leu Asn Arg Cys Gln Leu Lys His Thr Ile Ala Leu Trp Gln Phe Leu
    370                 375                 380
Ser Ala His Lys Ser Glu Gln Leu Leu Arg Leu His Lys Glu Pro Phe
385                 390                 395                 400
Gly Glu Ile Ser Ser Arg Tyr Lys Ala Asp Leu Ser Pro Glu Asn Ala
                405                 410                 415
Lys Leu Leu Ser Thr Phe Leu Asn Gln Thr Gly Leu Asp Ala Phe Leu
            420                 425                 430
Leu Glu Leu His Glu Met Ile Ile Leu Lys Leu Lys Asn Pro Gln Thr
        435                 440                 445
Gln Thr Glu Glu Arg Phe Arg Pro Gln Trp Ser Leu Arg Asp Thr Leu
    450                 455                 460
Val Ser Tyr Met Gln Thr Lys Glu Ser Glu Ile Leu Pro Glu Met Ala
465                 470                 475                 480
Ser Gln Phe Pro Glu Glu Ile Leu Leu Ala Ser Cys Val Ser Val Trp
                485                 490                 495
Lys Thr Ala Ala Val Leu Lys Trp Asn Arg Glu Met Arg
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<210> 57
<211> 1760
<212> DNA
<213> Homo sapiens

<400> 57
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tggcgtctgt cctcaccatg cctagccttt gggaccgctt ctcgtcgtcg tccacctcct 240
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<210> 58
<211> 232
<212> PRT
<213> Homo sapiens

<400> 58
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Pro Ser Ser Leu Pro Arg Thr Pro Thr Pro Asp Arg Pro Pro Arg Ser
20 25 30
Ala Trp Gly Ser Ala Thr Arg Glu Glu Gly Phe Asp Arg Ser Thr Ser
35 40 45
Leu Glu Ser Ser Asp Cys Glu Ser Leu Asp Ser Ser Asn Ser Gly Phe
50 55 60
Gly Pro Glu Glu Asp Thr Ala Tyr Leu Asp Gly Val Ser Leu Pro Asp
65 70 75 80
Phe Glu Leu Leu Ser Asp Pro Glu Asp Glu His Leu Cys Ala Asn Leu
85 90 95
Met Gln Leu Leu Gln Glu Ser Leu Ala Gln Ala Arg Leu Gly Ser Arg
100 105 110

Arg Pro Ala Arg Leu Leu Met Pro Ser Gln Leu Val Ser Gln Val Gly
115 120 125
Lys Glu Leu Leu Arg Leu Ala Tyr Ser Glu Pro Cys Gly Leu Arg Gly
130 135 140
Ala Leu Leu Asp Val Cys Val Glu Gln Gly Lys Ser Cys His Ser Val
145 150 155 160
Gly Gln Leu Ala Leu Asp Pro Ser Leu Val Pro Thr Phe Gln Leu Thr
165 170 175
Leu Val Leu Arg Leu Asp Ser Arg Leu Trp Pro Lys Ile Gln Gly Leu
180 185 190
Phe Ser Ser Ala Asn Ser Pro Phe Leu Pro Gly Phe Ser Gln Ser Leu
195 200 205
Thr Leu Ser Thr Gly Phe Arg Val Ile Lys Lys Lys Leu Tyr Ser Ser
210 215 220
Glu Gln Leu Leu Ile Glu Glu Cys
225 230

<210> 59
<211> 2012
<212> DNA
<213> Homo sapiens

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa 2012

<210> 60
<211> 495
<212> PRT
<213> Homo sapiens

<400> 60
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20 25 30
Arg Val Arg Ala Leu Asn Asp Gly Gly Tyr Gly Pro Tyr Ser Asp Val
35 40 45
Ser Glu Ile Thr Thr Ala Ala Gly Pro Pro Gly Gln Cys Lys Ala Pro
50 55 60
Cys Ile Ser Cys Thr Pro Asp Gly Cys Val Leu Val Gly Trp Glu Ser
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Cys Gln Thr Pro Ala Ser Ala Pro Asp Pro Val Ser Thr Leu Cys Val
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Cys Ala Cys Arg Arg Cys Leu Asp Thr Ser Gln Glu Leu Ser Gly Ala

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<211> 2384
<212> DNA
<213> Homo sapiens

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<212> PRT
<213> Homo sapiens

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275 280 285
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Gly Leu Glu Pro Gly Thr Glu Tyr Thr Ile Tyr Val Ile Ala Leu Lys
370 375 380
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<211> 7680
<212> DNA
<213> Homo sapiens

<400> 63

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gtgccaaagc tttactactg tggaaagaca actgttttaa taaaagattt acattccaca 7680


<210> 64
<211> 2328
<212> PRT
<213> Homo sapiens

<400> 64
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            20                  25                  30
Gln Ile Asn Gln Gln Trp Glu Arg Thr Tyr Leu Gly Asn Val Leu Val
        35                  40                  45
Cys Thr Cys Tyr Gly Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro
    50                  55                  60
Glu Ala Glu Glu Thr Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg
65                  70                  75                  80
Val Gly Asp Thr Tyr Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys
                85                  90                  95
Thr Cys Ile Gly Ala Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn
            100                 105                 110
Arg Cys His Glu Gly Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg
        115                 120                 125
Arg Pro His Glu Thr Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly
    130                 135                 140
Asn Gly Lys Gly Glu Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe
145                 150                 155                 160
Asp His Ala Ala Gly Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys
                165                 170                 175
Pro Tyr Gln Gly Trp Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly
            180                 185                 190
Ser Gly Arg Ile Thr Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp
        195                 200                 205
Thr Arg Thr Ser Tyr Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn
    210                 215                 220
Arg Gly Asn Leu Leu Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu
225                 230                 235                 240
Trp Lys Cys Glu Arg His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser
                245                 250                 255
Gly Pro Phe Thr Asp Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His
            260                 265                 270
Pro Gln Pro Pro Pro Tyr Gly His Cys Val Thr Asp Ser Gly Val Val
        275                 280                 285
Tyr Ser Val Gly Met Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met
    290                 295                 300
Leu Cys Thr Cys Leu Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val
305                 310                 315                 320
Thr Gln Thr Tyr Gly Gly Asn Leu Asn Gly Glu Pro Cys Val Leu Pro
                325                 330                 335
Phe Thr Tyr Asn Gly Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg
            340                 345                 350
Gln Asp Gly His Leu Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp
        355                 360                 365
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Gln Lys Tyr Ser Phe Cys Thr Asp His Thr Val Leu Val Gln Thr Gln
    370                 375                 380
Gly Gly Asn Ser Asn Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn
385                 390                 395                 400
Asn His Asn Tyr Thr Asp Cys Thr Ser Glu Gly Arg Arg Asp Asn Met
                405                 410                 415
Lys Trp Cys Gly Thr Thr Gln Asn Tyr Asp Ala Asp Gln Lys Phe Gly
            420                 425                 430
Phe Cys Pro Met Ala Ala His Glu Glu Ile Cys Thr Thr Asn Glu Gly
        435                 440                 445
Val Met Tyr Arg Ile Gly Asp Gln Trp Asp Lys Gln His Asp Met Gly
    450                 455                 460
His Met Met Arg Cys Thr Cys Val Gly Asn Gly Arg Gly Glu Trp Thr
465                 470                 475                 480
Cys Ile Ala Tyr Ser Gln Leu Arg Asp Gln Cys Ile Val Asp Asp Ile
                485                 490                 495
Thr Tyr Asn Val Asn Asp Thr Phe His Lys Arg His Glu Glu Gly His
            500                 505                 510
Met Leu Asn Cys Thr Cys Phe Gly Gln Gly Arg Gly Arg Trp Lys Cys
        515                 520                 525
Asp Pro Val Asp Gln Cys Gln Asp Ser Glu Thr Gly Thr Phe Tyr Gln
    530                 535                 540
Ile Gly Asp Ser Trp Glu Lys Tyr Val His Gly Val Arg Tyr Gln Cys
545                 550                 555                 560
Tyr Cys Tyr Gly Arg Gly Ile Gly Glu Trp His Cys Gln Pro Leu Gln
                565                 570                 575
Thr Tyr Pro Ser Ser Ser Gly Pro Val Glu Val Phe Ile Thr Glu Thr
            580                 585                 590
Pro Ser Gln Pro Asn Ser His Pro Ile Gln Trp Asn Ala Pro Gln Pro
        595                 600                 605
Ser His Ile Ser Lys Tyr Ile Leu Arg Trp Arg Pro Lys Asn Ser Val
    610                 615                 620
Gly Arg Trp Lys Glu Ala Thr Ile Pro Gly His Leu Asn Ser Tyr Thr
625                 630                 635                 640
Ile Lys Gly Leu Lys Pro Gly Val Val Tyr Glu Gly Gln Leu Ile Ser
                645                 650                 655
Ile Gln Gln Tyr Gly His Gln Glu Val Thr Arg Phe Asp Phe Thr Thr
            660                 665                 670
Thr Ser Thr Ser Thr Pro Val Thr Ser Asn Thr Val Thr Gly Glu Thr
        675                 680                 685
Thr Pro Phe Ser Pro Leu Val Ala Thr Ser Glu Ser Val Thr Glu Ile
    690                 695                 700
Thr Ala Ser Ser Phe Val Val Ser Trp Val Ser Ala Ser Asp Thr Val
705                 710                 715                 720
Ser Gly Phe Arg Val Glu Tyr Glu Leu Ser Glu Glu Gly Asp Glu Pro
                725                 730                 735
Gln Tyr Leu Asp Leu Pro Ser Thr Ala Thr Ser Val Asn Ile Pro Asp
            740                 745                 750
Leu Leu Pro Gly Arg Lys Tyr Ile Val Asn Val Tyr Gln Ile Ser Glu
        755                 760                 765
Asp Gly Glu Gln Ser Leu Ile Leu Ser Thr Ser Gln Thr Thr Ala Pro
    770                 775                 780
Asp Ala Pro Pro Asp Pro Thr Val Asp Gln Val Asp Asp Thr Ser Ile
785                 790                 795                 800
Val Val Arg Trp Ser Arg Pro Gln Ala Pro Ile Thr Gly Tyr Arg Ile
                805                 810                 815
Val Tyr Ser Pro Ser Val Glu Gly Ser Ser Thr Glu Leu Asn Leu Pro
            820                 825                 830
Glu Thr Ala Asn Ser Val Thr Leu Ser Asp Leu Gln Pro Gly Val Gln
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            835                 840                 845
Tyr Asn Ile Thr Ile Tyr Ala Val Glu Glu Asn Gln Glu Ser Thr Pro
        850                 855                 860
Val Val Ile Gln Gln Glu Thr Thr Gly Thr Pro Arg Ser Asp Thr Val
865                 870                 875                 880
Pro Ser Pro Arg Asp Leu Gln Phe Val Glu Val Thr Asp Val Lys Val
                885                 890                 895
Thr Ile Met Trp Thr Pro Pro Glu Ser Ala Val Thr Gly Tyr Arg Val
            900                 905                 910
Asp Val Ile Pro Val Asn Leu Pro Gly Glu His Gly Gln Arg Leu Pro
        915                 920                 925
Ile Ser Arg Asn Thr Phe Ala Glu Val Thr Gly Leu Ser Pro Gly Val
    930                 935                 940
Thr Tyr Tyr Phe Lys Val Phe Ala Val Ser His Gly Arg Glu Ser Lys
945                 950                 955                 960
Pro Leu Thr Ala Gln Gln Thr Thr Lys Leu Asp Ala Pro Thr Asn Leu
                965                 970                 975
Gln Phe Val Asn Glu Thr Asp Ser Thr Val Leu Val Arg Trp Thr Pro
            980                 985                 990
Pro Arg Ala Gln Ile Thr Gly Tyr Arg Leu Thr Val Gly Leu Thr Arg
        995                 1000                1005
Arg Gly Gln Pro Arg Gln Tyr Asn Val Gly Pro Ser Val Ser Lys Tyr
    1010                1015                1020
Pro Leu Arg Asn Leu Gln Pro Ala Ser Glu Tyr Thr Val Ser Leu Val
1025                1030                1035                1040
Ala Ile Lys Gly Asn Gln Glu Ser Pro Lys Ala Thr Gly Val Phe Thr
                1045                1050                1055
Thr Leu Gln Pro Gly Ser Ser Ile Pro Pro Tyr Asn Thr Glu Val Thr
            1060                1065                1070
Glu Thr Thr Ile Val Ile Thr Trp Thr Pro Ala Pro Arg Ile Gly Phe
        1075                1080                1085
Lys Leu Gly Val Arg Pro Ser Gln Gly Gly Glu Ala Pro Arg Glu Val
    1090                1095                1100
Thr Ser Asp Ser Gly Ser Ile Val Val Ser Gly Leu Thr Pro Gly Val
1105                1110                1115                1120
Glu Tyr Val Tyr Thr Ile Gln Val Leu Arg Asp Gly Gln Glu Arg Asp
                1125                1130                1135
Ala Pro Ile Val Asn Lys Val Val Thr Pro Leu Ser Pro Pro Thr Asn
            1140                1145                1150
Leu His Leu Glu Ala Asn Pro Asp Thr Gly Val Leu Thr Val Ser Trp
        1155                1160                1165
Glu Arg Ser Thr Thr Pro Asp Ile Thr Gly Tyr Arg Ile Thr Thr Thr
    1170                1175                1180
Pro Thr Asn Gly Gln Gln Gly Asn Ser Leu Glu Glu Val Val His Ala
1185                1190                1195                1200
Asp Gln Ser Ser Cys Thr Phe Asp Asn Leu Ser Pro Gly Leu Glu Tyr
                1205                1210                1215
Asn Val Ser Val Tyr Thr Val Lys Asp Asp Lys Glu Ser Val Pro Ile
            1220                1225                1230
Ser Asp Thr Ile Ile Pro Ala Val Pro Pro Pro Thr Asp Leu Arg Phe
        1235                1240                1245
Thr Asn Ile Gly Pro Asp Thr Met Arg Val Thr Trp Ala Pro Pro Pro
    1250                1255                1260
Ser Ile Asp Leu Thr Asn Phe Leu Val Arg Tyr Ser Pro Val Lys Asn
1265                1270                1275                1280
Glu Glu Asp Val Ala Glu Leu Ser Ile Ser Pro Ser Asp Asn Ala Val
                1285                1290                1295
Val Leu Thr Asn Leu Leu Pro Gly Thr Glu Tyr Val Val Ser Val Ser
            1300                1305                1310
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Ser Val Tyr Glu Gln His Glu Ser Thr Pro Leu Arg Gly Arg Gln Lys
1315 1320 1325
Thr Gly Leu Asp Ser Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala
1330 1335 1340
Asn Ser Phe Thr Val His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly
1345 1350 1355 1360
Tyr Arg Ile Arg His His Pro Glu His Phe Ser Gly Arg Pro Arg Glu
1365 1370 1375
Asp Arg Val Pro His Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr
1380 1385 1390
Pro Gly Thr Glu Tyr Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu
1395 1400 1405
Glu Ser Pro Leu Leu Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro
1410 1415 1420
Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
1425 1430 1435 1440
Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly
1445 1450 1455
Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser
1460 1465 1470
Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
1475 1480 1485
Ile Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser
1490 1495 1500
Lys Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
1505 1510 1515 1520
Met Gln Val Thr Asp Val Gln Asp Asn Ser Ile Ser Val Lys Trp Leu
1525 1530 1535
Pro Ser Ser Ser Pro Val Thr Gly Tyr Arg Val Thr Thr Thr Pro Lys
1540 1545 1550
Asn Gly Pro Gly Pro Thr Lys Thr Lys Thr Ala Gly Pro Asp Gln Thr
1555 1560 1565
Glu Met Thr Ile Glu Gly Leu Gln Pro Thr Val Glu Tyr Val Val Ser
1570 1575 1580
Val Tyr Ala Gln Asn Pro Ser Gly Glu Ser Gln Pro Leu Val Gln Thr
1585 1590 1595 1600
Ala Val Thr Asn Ile Asp Arg Pro Lys Gly Leu Ala Phe Thr Asp Val
1605 1610 1615
Asp Val Asp Ser Ile Lys Ile Ala Trp Glu Ser Pro Gln Gly Gln Val
1620 1625 1630
Ser Arg Tyr Arg Val Thr Tyr Ser Ser Pro Glu Asp Gly Ile His Glu
1635 1640 1645
Leu Phe Pro Ala Pro Asp Gly Glu Glu Asp Thr Ala Glu Leu Gln Gly
1650 1655 1660
Leu Arg Pro Gly Ser Glu Tyr Thr Val Ser Val Val Ala Leu His Asp
1665 1670 1675 1680
Asp Met Glu Ser Gln Pro Leu Ile Gly Thr Gln Ser Thr Ala Ile Pro
1685 1690 1695
Ala Pro Thr Asp Leu Lys Phe Thr Gln Val Thr Pro Thr Ser Leu Ser
1700 1705 1710
Ala Gln Trp Thr Pro Pro Asn Val Gln Leu Thr Gly Tyr Arg Val Arg
1715 1720 1725
Val Thr Pro Lys Glu Lys Thr Gly Pro Met Lys Glu Ile Asn Leu Ala
1730 1735 1740
Pro Asp Ser Ser Ser Val Val Val Ser Gly Leu Met Val Ala Thr Lys
1745 1750 1755 1760
Tyr Glu Val Ser Val Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro
1765 1770 1775
Ala Gln Gly Val Val Thr Thr Leu Glu Asn Val Ser Pro Pro Arg Arg

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            1780                1785                1790
Ala Arg Val Thr Asp Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp Arg
        1795                1800                1805
Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln Val Asp Ala Val Pro Ala
    1810                1815                1820
Asn Gly Gln Thr Pro Ile Gln Arg Thr Ile Lys Pro Asp Val Arg Ser
1825                1830                1835                1840
Tyr Thr Ile Thr Gly Leu Gln Pro Gly Thr Asp Tyr Lys Ile Tyr Leu
                1845                1850                1855
Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val Val Ile Asp Ala
            1860                1865                1870
Ser Thr Ala Ile Asp Ala Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr
        1875                1880                1885
Pro Asn Ser Leu Leu Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr
    1890                1895                1900
Gly Tyr Ile Ile Lys Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val
1905                1910                1915                1920
Val Pro Arg Pro Arg Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu
                1925                1930                1935
Glu Pro Gly Thr Glu Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn
            1940                1945                1950
Gln Lys Ser Glu Pro Leu Ile Gly Arg Lys Lys Thr Asp Glu Leu Pro
        1955                1960                1965
Gln Leu Val Thr Leu Pro His Pro Asn Leu His Gly Pro Glu Ile Leu
    1970                1975                1980
Asp Val Pro Ser Thr Val Gln Lys Thr Pro Phe Val Thr His Pro Gly
1985                1990                1995                2000
Tyr Asp Thr Gly Asn Gly Ile Gln Leu Pro Gly Thr Ser Gly Gln Gln
                2005                2010                2015
Pro Ser Val Gly Gln Gln Met Ile Phe Glu Glu His Gly Phe Arg Arg
            2020                2025                2030
Thr Thr Pro Pro Thr Thr Ala Thr Pro Ile Arg His Arg Pro Arg Pro
        2035                2040                2045
Tyr Pro Pro Asn Val Gly Gln Glu Ala Leu Ser Gln Thr Thr Ile Ser
    2050                2055                2060
Trp Ala Pro Phe Gln Asp Thr Ser Glu Tyr Ile Ile Ser Cys His Pro
2065                2070                2075                2080
Val Gly Thr Asp Glu Glu Pro Leu Gln Phe Arg Val Pro Gly Thr Ser
                2085                2090                2095
Thr Ser Ala Thr Leu Thr Gly Leu Thr Arg Gly Ala Thr Tyr Asn Ile
            2100                2105                2110
Ile Val Glu Ala Leu Lys Asp Gln Gln Arg His Lys Val Arg Glu Glu
        2115                2120                2125
Val Val Thr Val Gly Asn Ser Val Asn Glu Gly Leu Asn Gln Pro Thr
    2130                2135                2140
Asp Asp Ser Cys Phe Asp Pro Tyr Thr Val Ser His Tyr Ala Val Gly
2145                2150                2155                2160
Asp Glu Trp Glu Arg Met Ser Glu Ser Gly Phe Lys Leu Leu Cys Gln
                2165                2170                2175
Cys Leu Gly Phe Gly Ser Gly His Phe Arg Cys Asp Ser Ser Arg Trp
            2180                2185                2190
Cys His Asp Asn Gly Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg
        2195                2200                2205
Gln Gly Glu Asn Gly Gln Met Met Ser Cys Thr Cys Leu Gly Asn Gly
    2210                2215                2220
Lys Gly Glu Phe Lys Cys Asp Pro His Glu Ala Thr Cys Tyr Asp Asp
2225                2230                2235                2240
Gly Lys Thr Tyr His Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu Gly
                2245                2250                2255
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Ala Ile Cys Ser Cys Thr Cys Phe Gly Gly Gln Arg Gly Trp Arg Cys
2260 2265 2270
Asp Asn Cys Arg Arg Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr
2275 2280 2285
Gly Gln Ser Tyr Asn Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn
2290 2295 2300
Thr Asn Val Asn Cys Pro Ile Glu Cys Phe Met Pro Leu Asp Val Gln
2305 2310 2315 2320
Ala Asp Arg Glu Asp Ser Arg Glu
2325

<210> 65
<211> 1844
<212> DNA
<213> Homo sapiens

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aagggacgct cgggggacgc tgttcctgag gtgtcgccgc ctccctgtcc tcgccctccg 180
cggtgggga gaaacccagg agcgaagccc agagcccgcg gcgcggccgg cggacgaacg 240
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cccggggcag cagcggctct cctgcgcacg ccgagtccta ctccagcggc ggcggcggcc 420
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aggcggagac agaggagctg gaggaggaga agtcaggcct gcagaaggag attgctgagc 840
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<210> 66
<211> 326
<212> PRT
<213> Homo sapiens

<400> 66
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Ser Gly Ser Pro Ala His Ala Glu Ser Tyr Ser Ser Gly Gly Gly Gly

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            35                  40                  45
Pro Thr Ile Asn Ala Ile Thr Thr Ser Gln Asp Leu Gln Trp Met Val
    50                  55                  60
Gln Pro Thr Val Ile Thr Ser Met Ser Asn Pro Tyr Pro Arg Ser His
65                  70                  75                  80
Pro Tyr Ser Pro Leu Pro Gly Leu Ala Ser Val Pro Gly His Met Ala
                85                  90                  95
Leu Pro Arg Pro Gly Val Ile Lys Thr Ile Gly Thr Thr Val Gly Arg
            100                 105                 110
Arg Arg Arg Asp Glu Gln Leu Ser Pro Glu Glu Glu Glu Lys Arg Arg
        115                 120                 125
Ile Arg Arg Glu Arg Asn Lys Leu Ala Ala Ala Lys Cys Arg Asn Arg
    130                 135                 140
Arg Arg Glu Leu Thr Glu Lys Leu Gln Ala Glu Thr Glu Glu Leu Glu
145                 150                 155                 160
Glu Glu Lys Ser Gly Leu Gln Lys Glu Ile Ala Glu Leu Gln Lys Glu
                165                 170                 175
Lys Glu Lys Leu Glu Phe Met Leu Val Ala His Gly Pro Val Cys Lys
            180                 185                 190
Ile Ser Pro Glu Glu Arg Arg Ser Pro Pro Ala Pro Gly Leu Gln Pro
        195                 200                 205
Met Arg Ser Gly Gly Gly Ser Val Gly Ala Val Val Val Lys Gln Glu
    210                 215                 220
Pro Leu Glu Glu Asp Ser Pro Ser Ser Ser Ser Ala Gly Leu Asp Lys
225                 230                 235                 240
Ala Gln Arg Ser Val Ile Lys Pro Ile Ser Ile Ala Gly Gly Phe Tyr
                245                 250                 255
Gly Glu Glu Pro Leu His Thr Pro Ile Val Val Thr Ser Thr Pro Ala
            260                 265                 270
Val Thr Pro Gly Thr Ser Asn Leu Val Phe Thr Tyr Pro Ser Val Leu
        275                 280                 285
Glu Gln Glu Ser Pro Ala Ser Pro Ser Glu Ser Cys Ser Lys Ala His
    290                 295                 300
Arg Arg Ser Ser Ser Ser Gly Asp Gln Ser Ser Asp Ser Leu Asn Ser
305                 310                 315                 320
Pro Thr Leu Leu Ala Leu
                325


<210> 67
<211> 3602
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 2087, 2093, 2098
<223> n = A,T,C or G

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aagggacgct cgggggacgc tgttcctgag gtgtcgccgc ctccctgtcc tcgccctccg 180
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cccggggcag cagcggctct cctgcgcacg ccgagtccta ctccagcggc ggcggcggcc 420
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<212> DNA
<213> Homo sapiens

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<211> 756
<212> PRT
<213> Homo sapiens

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Lys Gln Asp Pro Ser Asn Ser Lys Asn Ile Ser Lys His Gly Gln Asn
        35                  40                  45
Asn Pro Val Gly Asp Tyr Glu His Ala Asp Asp Gln Ala Glu Glu Asp
    50                  55                  60
Ala Leu Gln Met Ala Val Gly Tyr Phe Glu Lys Gly Pro Ile Lys Ala
65                  70                  75                  80
Ser Gln Asn Lys Asp Lys Thr Leu Glu Lys His Leu Lys Thr Val Glu
                85                  90                  95
Asn Val Ala Trp Lys Asn Gly Leu Ala Ser Glu Glu Ile Asp Ile Leu
            100                 105                 110
Leu Asn Ile Ala Leu Ser Gly Lys Phe Gly Asn Ala Val Asn Thr Arg
        115                 120                 125
Ile Leu Lys Cys Met Ile Pro Ala Thr Val Ile Ser Glu Asp Ser Val
    130                 135                 140
Val Lys Ala Val Ser Trp Leu Cys Val Gly Lys Cys Ser Gly Ser Thr
145                 150                 155                 160
Lys Val Leu Phe Tyr Arg Trp Leu Val Ala Met Phe Asp Phe Ile Asp
                165                 170                 175
Arg Lys Glu Gln Ile Asn Leu Leu Tyr Gly Phe Phe Phe Ala Ser Leu
            180                 185                 190
Gln Asp Asp Ala Leu Cys Pro Tyr Val Cys His Leu Leu Tyr Leu Leu
        195                 200                 205
Thr Lys Lys Glu Asn Val Lys Pro Phe Arg Val Arg Lys Leu Leu Asp
    210                 215                 220
Leu Gln Ala Lys Met Gly Met Gln Pro His Leu Gln Ala Leu Leu Ser
225                 230                 235                 240
Leu Tyr Lys Phe Phe Ala Pro Ala Leu Ile Ser Val Ser Leu Pro Val
                245                 250                 255
Arg Lys Lys Ile Tyr Leu Gln Asn Ser Glu Asn Leu Trp Lys Thr Ala
            260                 265                 270
Leu Leu Ala Val Lys Gln Arg Asn Arg Gly Pro Ser Pro Glu Pro Leu
        275                 280                 285
Lys Leu Met Leu Gly Pro Ala Asn Val Arg Pro Leu Lys Arg Lys Trp
    290                 295                 300
Asn Ser Leu Ser Val Ile Pro Val Leu Asn Ser Ser Ser Tyr Thr Lys
305                 310                 315                 320
Glu Cys Gly Lys Lys Glu Met Ser Leu Ser Asp Cys Leu Asn Arg Ser
                325                 330                 335
Gly Ser Phe Pro Leu Glu Gln Leu Gln Ser Phe Pro Gln Leu Leu Gln
            340                 345                 350
Asn Ile His Cys Leu Glu Leu Pro Ser Gln Met Gly Ser Val Leu Asn
        355                 360                 365
Asn Ser Leu Leu Leu His Tyr Ile Asn Cys Val Arg Asp Glu Pro Val
    370                 375                 380
Leu Leu Arg Phe His Tyr Trp Leu Ser Gln Thr Leu Gln Glu Glu Cys
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Phe Leu Asp Thr Ile Ile Arg Ala Glu Cys Phe Leu Gln Glu Gly Tyr
            420                 425                 430
Tyr Ser Cys Glu Ala Phe Leu Tyr Lys Ser Leu Pro Leu Trp Asp Gly
        435                 440                 445
Leu Ser Cys Arg Ser Gln Phe Leu Gln Leu Val Ser Trp Ile Pro Phe
    450                 455                 460
Ser Ser Phe Ser Glu Val Lys Pro Leu Leu Phe Asp His Leu Ala Gln
465                 470                 475                 480
Leu Phe Phe Thr Ser Thr Ile Tyr Phe Lys Cys Ser Val Leu Gln Ser
                485                 490                 495
Leu Lys Glu Leu Leu Gln Asn Trp Leu Leu Trp Leu Ser Met Asp Ile
            500                 505                 510
His Met Lys Pro Val Thr Asn Ser Pro Leu Glu Thr Thr Leu Gly Gly
        515                 520                 525
Ser Met Asn Cys Val Ser Lys Leu Ile His Tyr Val Gly Trp Leu Ser
    530                 535                 540
Thr Thr Ala Met Arg Leu Glu Ser Asn Asn Thr Phe Leu Leu His Phe
545                 550                 555                 560
Ile Leu Asp Phe Tyr Glu Lys Val Cys Asp Ile Tyr Ile Asn Tyr Asp
                565                 570                 575
Leu Pro Leu Val Val Leu Phe Pro Pro Gly Ile Phe Tyr Ser Ala Leu
            580                 585                 590
Leu Ser Leu Asp Thr Ser Ile Leu Asn Gln Leu Cys Phe Ile Met His
        595                 600                 605
Arg Tyr Arg Lys Asn Leu Thr Ala Ala Lys Lys Asn Glu Leu Val Gln
    610                 615                 620
Lys Thr Lys Ser Glu Phe Asn Phe Ser Ser Lys Thr Tyr Gln Glu Phe
625                 630                 635                 640
Asn Tyr Tyr Leu Thr Ser Met Val Gly Cys Leu Trp Thr Ser Lys Pro
                645                 650                 655
Phe Ala Lys Gly Ile Tyr Ile Asp Pro Glu Ile Leu Glu Lys Thr Gly
            660                 665                 670
Val Ala Glu Tyr Lys Asn Ser Leu Asn Val Val His His Pro Ser Phe
        675                 680                 685
Leu Ser Tyr Ala Val Ser Phe Leu Leu Gln Glu Ser Pro Glu Glu Arg
    690                 695                 700
Thr Val Asn Val Ser Ser Ile Arg Gly Lys Lys Trp Ser Trp Tyr Leu
705                 710                 715                 720
Asp Tyr Leu Phe Ser Gln Gly Leu Gln Gly Leu Lys Leu Phe Ile Arg
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Ser Ser Val His His Ser Ser Ile Pro Arg Ala Glu Gly Ile Asn Cys
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Asn Asn Gln Tyr
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<210> 70
<211> 1559
<212> DNA
<213> Homo sapiens

<400> 70

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atctcttcct tttcctcctc atcttttctc ccttcccgct tttttcctct tccttcaaag 180
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<210> 71
<211> 338
<212> PRT
<213> Homo sapiens

<400> 71

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            20                  25                  30
Gly Val Asn Asp Ser Phe Pro Asp Gly Asp Tyr Asp Ala Asn Leu Glu
        35                  40                  45
Ala Ala Ala Pro Cys His Ser Cys Asn Leu Leu Asp Asp Ser Ala Leu
    50                  55                  60
Pro Phe Phe Ile Leu Thr Ser Val Leu Gly Ile Leu Ala Ser Ser Thr
65                  70                  75                  80
Val Leu Phe Met Leu Phe Arg Pro Leu Phe Arg Trp Gln Leu Cys Pro
                85                  90                  95
Gly Trp Pro Val Leu Ala Gln Leu Ala Val Gly Ser Ala Leu Phe Ser
            100                 105                 110
Ile Val Val Pro Val Leu Ala Pro Gly Leu Gly Ser Thr Arg Ser Ser
        115                 120                 125
Ala Leu Cys Ser Leu Gly Tyr Cys Val Trp Tyr Gly Ser Ala Phe Ala
    130                 135                 140
Gln Ala Leu Leu Leu Gly Cys His Ala Ser Leu Gly His Arg Leu Gly
145                 150                 155                 160
Ala Gly Gln Val Pro Gly Leu Thr Leu Gly Leu Thr Val Gly Ile Trp
                165                 170                 175
Gly Val Ala Ala Leu Leu Thr Leu Pro Val Thr Leu Ala Ser Gly Ala
            180                 185                 190
Ser Gly Gly Leu Cys Thr Leu Ile Tyr Ser Thr Glu Leu Lys Ala Leu
        195                 200                 205
Gln Ala Thr His Thr Val Ala Cys Leu Ala Ile Phe Val Leu Leu Pro
    210                 215                 220
Leu Gly Leu Phe Gly Ala Lys Gly Leu Lys Lys Ala Leu Gly Met Gly
225                 230                 235                 240
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Pro Gly Pro Trp Met Asn Ile Leu Trp Ala Trp Phe Ile Phe Trp Trp
245 250 255
Pro His Gly Val Val Leu Gly Leu Asp Phe Leu Val Arg Ser Lys Leu
260 265 270
Leu Leu Leu Ser Thr Cys Leu Ala Gln Gln Ala Leu Asp Leu Leu Leu
275 280 285
Asn Leu Ala Glu Ala Leu Ala Ile Leu His Cys Val Ala Thr Pro Leu
290 295 300
Leu Leu Ala Leu Phe Cys His Gln Ala Thr Arg Thr Leu Leu Pro Ser
305 310 315 320
Leu Pro Leu Pro Glu Gly Trp Ser Ser His Leu Asp Thr Leu Gly Ser
325 330 335
Lys Ser

<210> 72
<211> 817
<212> DNA
<213> Homo sapiens

<400> 72
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<210> 73
<211> 130
<212> PRT
<213> Homo sapiens

<400> 73
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20 25 30
Asp Ser Gly Ser Gly Phe Trp Lys Ala Leu Thr Phe Met Ala Val Gly
35 40 45
Gly Gly Leu Ala Val Ala Gly Leu Pro Ala Leu Gly Phe Thr Gly Ala
50 55 60
Gly Ile Ala Ala Asn Ser Val Ala Ala Ser Leu Met Ser Trp Ser Ala
65 70 75 80
Ile Leu Asn Gly Gly Gly Val Pro Ala Gly Gly Leu Val Ala Thr Leu
85 90 95
Gln Ser Leu Gly Ala Gly Gly Ser Ser Val Val Ile Gly Asn Ile Gly
100 105 110
Ala Leu Met Gly Tyr Ala Thr His Lys Tyr Leu Asp Ser Glu Glu Asp
115 120 125

Glu Glu
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<210> 74
<211> 2861
<212> DNA
<213> Homo sapiens

<400> 74
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<210> 75
<211> 187
<212> PRT
<213> Homo sapiens

<400> 75
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Glu Ile Val Asp Gln Leu Glu Val Glu Ile Arg Asn Met Thr Leu Leu
            20                  25                  30
Val Glu Lys Leu Glu Thr Leu Asp Lys Asn Asn Val Leu Ala Ile Arg
        35                  40                  45
Arg Glu Ile Val Ala Leu Lys Thr Lys Leu Lys Glu Cys Glu Ala Ser
    50                  55                  60
Lys Asp Gln Asn Thr Pro Val Val His Pro Pro Pro Thr Pro Gly Ser
65                  70                  75                  80
Cys Gly His Gly Gly Val Val Asn Ile Ser Lys Pro Ser Val Val Gln
                85                  90                  95
Leu Asn Trp Arg Gly Phe Ser Tyr Leu Tyr Gly Ala Trp Gly Arg Asp
            100                 105                 110
Tyr Ser Pro Gln His Pro Asn Lys Gly Leu Tyr Trp Val Ala Pro Leu
        115                 120                 125
Asn Thr Asp Gly Arg Leu Leu Glu Tyr Tyr Ile Leu Tyr Asn Thr Leu
    130                 135                 140
Asp Asp Leu Leu Leu Tyr Ile Asn Ala Arg Glu Leu Arg Ile Thr Tyr
145                 150                 155                 160
Gly Gln Gly Ser Gly Thr Ala Val Tyr Asn Asn Asn Met Tyr Val Asn
                165                 170                 175
Met Tyr Thr Pro Gly Ile Leu Pro Glu Leu Thr
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<210> 76
<211> 956
<212> DNA
<213> Homo sapiens

<400> 76
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<210> 77
<211> 266
<212> PRT
<213> Homo sapiens

<400> 77
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35 40 45
Leu Ala Tyr Leu Lys Lys Asn His Glu Glu Glu Met Asn Ala Leu Arg
50 55 60
Gly Gln Val Gly Gly Glu Ile Asn Val Glu Met Asp Ala Ala Pro Gly
65 70 75 80
Val Asp Leu Ser Arg Ile Leu Asn Glu Met Arg Asp Gln Tyr Glu Lys
85 90 95
Met Ala Glu Lys Asn Arg Lys Asp Ala Glu Asp Trp Phe Phe Ser Lys
100 105 110
Thr Glu Glu Leu Asn Arg Glu Val Ala Thr Asn Ser Glu Leu Val Gln
115 120 125
Ser Gly Lys Ser Glu Ile Ser Glu Leu Arg Arg Thr Met Gln Ala Leu
130 135 140
Glu Ile Glu Leu Gln Ser Gln Leu Ser Met Lys Ala Ser Leu Glu Gly
145 150 155 160
Asn Leu Ala Glu Thr Glu Asn Arg Tyr Cys Val Gln Leu Ser Gln Ile
165 170 175
Gln Gly Leu Ile Gly Ser Val Glu Glu Gln Leu Ala Gln Leu Arg Cys
180 185 190
Glu Met Glu Gln Gln Asn Gln Glu Tyr Lys Ile Leu Leu Asp Val Lys
195 200 205
Thr Arg Leu Glu Gln Glu Ile Ala Thr Tyr Arg Arg Leu Leu Glu Gly
210 215 220
Glu Asp Ala His Leu Thr Gln Tyr Lys Lys Glu Pro Val Thr Thr Arg
225 230 235 240
Gln Val Arg Thr Ile Val Glu Glu Val Gln Asp Gly Lys Val Ile Ser
245 250 255
Ser Arg Glu Gln Val His Gln Thr Thr Arg
260 265

<210> 78
<211> 1689
<212> DNA
<213> Homo sapiens

<400> 78
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gagacaatgt ctatgaattt cacctggagt tcttagacct tgtgaaacca gagcctgttt 360
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tgtatttctg ccagatgctg gcagttgtgg aaactatcaa tgcagcaatt ggagtcacta 780
cgtcaccggt gctgccttct ctgatccagc ttcttggaag aaattttatt ttgtttatca 840
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<210> 79
<211> 373
<212> PRT
<213> Homo sapiens

<400> 79
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            20                  25                  30
Ile Ser Ile Thr Glu Asn Val Leu His Phe Lys Ala Gln Gly His Gly
        35                  40                  45
Ala Lys Gly Asp Asn Val Tyr Glu Phe His Leu Glu Phe Leu Asp Leu
    50                  55                  60
Val Lys Pro Glu Pro Val Tyr Lys Leu Thr Gln Arg Gln Val Asn Ile
65                  70                  75                  80
Thr Val Gln Lys Lys Val Ser Gln Trp Trp Glu Arg Leu Thr Lys Gln
                85                  90                  95
Glu Lys Arg Pro Leu Phe Leu Ala Pro Asp Phe Asp Arg Trp Leu Asp
            100                 105                 110
Glu Ser Asp Ala Glu Met Glu Leu Arg Ala Lys Glu Glu Glu Arg Leu
        115                 120                 125
Asn Lys Leu Arg Leu Glu Ser Glu Gly Ser Pro Glu Thr Leu Thr Asn
    130                 135                 140
Leu Arg Lys Gly Tyr Leu Phe Met Tyr Asn Leu Val Gln Phe Leu Gly
145                 150                 155                 160
Phe Ser Trp Ile Phe Val Asn Leu Thr Val Arg Phe Cys Ile Leu Gly
                165                 170                 175
Lys Glu Ser Phe Tyr Asp Thr Phe His Thr Val Ala Asp Met Met Tyr
            180                 185                 190
Phe Cys Gln Met Leu Ala Val Val Glu Thr Ile Asn Ala Ala Ile Gly
        195                 200                 205
Val Thr Thr Ser Pro Val Leu Pro Ser Leu Ile Gln Leu Leu Gly Arg
    210                 215                 220
Asn Phe Ile Leu Phe Ile Ile Phe Gly Thr Met Glu Glu Met Gln Asn
225                 230                 235                 240
Lys Ala Val Val Phe Phe Val Phe Tyr Leu Trp Ser Ala Ile Glu Ile
                245                 250                 255
Phe Arg Tyr Ser Phe Tyr Met Leu Thr Cys Ile Asp Met Asp Trp Lys
            260                 265                 270
Val Leu Thr Trp Leu Arg Tyr Thr Leu Trp Ile Pro Leu Tyr Pro Leu
        275                 280                 285
Gly Cys Leu Val Glu Ala Val Ser Val Ile Gln Ser Ile Pro Ile Phe
    290                 295                 300
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Asn Glu Thr Gly Arg Phe Ser Phe Thr Leu Pro Tyr Pro Val Lys Ile
305 310 315 320
Lys Val Arg Phe Ser Phe Phe Leu Gln Ile Tyr Leu Ile Met Ile Phe
325 330 335
Leu Gly Leu Tyr Ile Asn Phe Arg His Leu Tyr Lys Gln Arg Arg Arg
340 345 350
Arg Tyr Gly Lys Lys Arg Lys Arg Ser Thr Lys Lys Lys Asp Leu Asp
355 360 365
Gly Phe Leu Pro Val
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<210> 80
<211> 1824
<212> DNA
<213> Homo sapiens

<400> 80
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<210> 81
<211> 142
<212> PRT
<213> Homo sapiens

<400> 81
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Val Arg Asp Asp Gly Ser Ala Val Ile Trp Val Thr Phe Lys Tyr Asp

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            20                  25                  30
Gly Ser Thr Ile Val Pro Gly Glu Gln Gly Ala Glu Tyr Gln His Phe
        35                  40                  45
Ile Gln Gln Cys Thr Asp Asp Val Arg Leu Phe Ala Phe Val Arg Phe
    50                  55                  60
Thr Thr Gly Asp Ala Met Ser Lys Arg Ser Lys Phe Ala Leu Ile Thr
65                  70                  75                  80
Trp Ile Gly Glu Asn Val Ser Gly Leu Gln Arg Ala Lys Thr Gly Thr
                85                  90                  95
Asp Lys Thr Leu Val Lys Glu Val Val Gln Asn Phe Ala Lys Glu Phe
            100                 105                 110
Val Ile Ser Asp Arg Lys Glu Leu Glu Glu Asp Phe Ile Lys Ser Glu
        115                 120                 125
Leu Lys Lys Ala Gly Gly Ala Asn Tyr Asp Ala Gln Thr Glu
    130                 135                 140


<210> 82
<211> 10174
<212> DNA
<213> Homo sapiens

<400> 82
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cagataaata ttgatgtcag catccttgaa ccatatcaaa gtgagcagtg tttggctact 9180
gcttctattt gaaatggtgc tgtgttttgg ttgtggtctg aagctttgaa gcgctactta 9240

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tacagaaact aataaagtat tctctaaata atga                             10174

&lt;210&gt; 83
&lt;211&gt; 2701
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 83
Met Ser Glu Lys Ser Gly Gln Ser Thr Lys Ala Lys Asp Gly Lys Lys
1               5                   10                  15
Tyr Ala Thr Leu Ser Leu Phe Asn Thr Tyr Lys Gly Lys Ser Leu Glu
            20                  25                  30
Thr Gln Lys Thr Thr Ala Arg His Gly Leu Gln Ser Leu Gly Lys Val
        35                  40                  45
Gly Ile Ser Arg Arg Met Pro Pro Pro Ala Asn Leu Pro Ser Leu Lys
    50                  55                  60
Ala Glu Asn Lys Gly Asn Asp Pro Asn Val Asn Ile Val Pro Lys Asp
65                  70                  75                  80
Gly Thr Gly Trp Ala Ser Lys Gln Glu Gln His Glu Glu Glu Lys Thr
                85                  90                  95
Pro Glu Val Pro Pro Ala Gln Pro Lys Pro Gly Val Ala Ala Pro Pro
            100                 105                 110
Glu Val Ala Pro Ala Pro Lys Ser Trp Ala Ser Asn Lys Gln Gly Gly
        115                 120                 125
Gln Gly Asp Gly Ile Gln Val Asn Ser Gln Phe Gln Gln Glu Phe Pro
    130                 135                 140
Ser Leu Gln Ala Ala Gly Asp Gln Glu Lys Lys Glu Lys Glu Thr Asn
145                 150                 155                 160
Asp Asp Asn Tyr Gly Pro Gly Pro Ser Leu Arg Pro Pro Asn Val Ala
                165                 170                 175
Cys Trp Arg Asp Gly Gly Lys Ala Ala Gly Ser Pro Ser Ser Ser Asp
            180                 185                 190
Gln Asp Glu Lys Leu Pro Gly Gln Asp Glu Ser Thr Ala Gly Thr Ser
        195                 200                 205
Glu Gln Asn Asp Ile Leu Lys Val Val Glu Lys Arg Ile Ala Cys Gly
    210                 215                 220
Pro Pro Gln Ala Lys Leu Asn Gly Gln Gln Ala Ala Leu Ala Ser Gln
225                 230                 235                 240
Tyr Arg Ala Met Met Pro Pro Tyr Met Phe Gln Gln Tyr Pro Arg Met
                245                 250                 255
Thr Tyr Pro Pro Leu His Gly Pro Met Arg Phe Pro Pro Ser Leu Ser
            260                 265                 270
Glu Thr Asn Lys Gly Leu Arg Gly Arg Gly Pro Pro Pro Ser Trp Ala
        275                 280                 285
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Ser Glu Pro Glu Arg Pro Ser Ile Leu Ser Ala Ser Glu Leu Lys Glu
    290                 295                 300
Leu Asp Lys Phe Asp Asn Leu Asp Ala Glu Ala Asp Glu Gly Trp Ala
305                 310                 315                 320
Gly Ala Gln Met Glu Val Asp Tyr Thr Glu Gln Leu Asn Phe Ser Asp
                325                 330                 335
Asp Asp Glu Gln Gly Ser Asn Ser Pro Lys Glu Asn Asn Ser Glu Asp
            340                 345                 350
Gln Gly Ser Lys Ala Ser Glu Asn Asn Glu Asn Lys Lys Glu Thr Asp
        355                 360                 365
Glu Val Ser Asn Thr Lys Ser Ser Ser Gln Ile Pro Ala Gln Pro Ser
    370                 375                 380
Val Ala Lys Val Pro Tyr Gly Lys Gly Pro Ser Phe Asn Gln Glu Arg
385                 390                 395                 400
Gly Thr Ser Ser His Leu Pro Pro Pro Pro Lys Leu Leu Ala Gln Gln
                405                 410                 415
His Pro Pro Pro Asp Arg Gln Ala Val Pro Gly Arg Pro Gly Pro Phe
            420                 425                 430
Pro Ser Lys Gln Gln Val Ala Asp Glu Asp Glu Ile Trp Lys Gln Arg
        435                 440                 445
Arg Arg Gln Gln Ser Glu Ile Ser Ala Ala Val Glu Arg Ala Arg Lys
    450                 455                 460
Arg Arg Glu Glu Glu Glu Arg Arg Met Glu Glu Gln Arg Lys Ala Ala
465                 470                 475                 480
Cys Ala Glu Lys Leu Lys Arg Leu Asp Glu Lys Leu Gly Ile Leu Glu
                485                 490                 495
Lys Gln Pro Ser Pro Glu Glu Ile Arg Glu Arg Glu Arg Glu Lys Glu
            500                 505                 510
Arg Glu Arg Glu Lys Glu Leu Glu Lys Glu Gln Glu Gln Glu Arg Glu
        515                 520                 525
Lys Glu Arg Glu Lys Asp Arg Glu Arg Gln Gln Glu Lys Glu Lys Glu
    530                 535                 540
Leu Glu Lys Glu Gln Glu Lys Gln Arg Glu Met Glu Lys Glu Arg Lys
545                 550                 555                 560
Gln Glu Lys Glu Lys Glu Leu Glu Arg Gln Lys Glu Lys Glu Lys Glu
                565                 570                 575
Leu Gln Lys Met Lys Glu Gln Glu Lys Glu Cys Glu Leu Glu Lys Glu
            580                 585                 590
Arg Glu Lys Leu Glu Glu Lys Ile Glu Pro Arg Glu Pro Asn Leu Glu
        595                 600                 605
Pro Met Val Glu Lys Gln Glu Ser Glu Asn Ser Cys Asn Lys Glu Glu
    610                 615                 620
Glu Pro Val Phe Thr Arg Gln Asp Ser Asn Arg Ser Glu Lys Glu Ala
625                 630                 635                 640
Thr Pro Val Val His Glu Thr Glu Pro Glu Ser Gly Ser Gln Pro Arg
                645                 650                 655
Pro Ala Val Leu Ser Gly Tyr Phe Lys Gln Phe Gln Lys Ser Leu Pro
            660                 665                 670
Pro Arg Phe Gln Arg Gln Gln Glu Gln Met Lys Gln Gln Gln Trp Gln
        675                 680                 685
Gln Gln Gln Gln Gln Gly Val Leu Pro Gln Thr Val Pro Ser Gln Pro
    690                 695                 700
Ser Ser Ser Thr Val Pro Pro Pro Pro His Arg Pro Leu Tyr Gln Pro
705                 710                 715                 720
Met Gln Pro His Pro Gln His Leu Ala Ser Met Gly Phe Asp Pro Arg
                725                 730                 735
Trp Leu Met Met Gln Ser Tyr Met Asp Pro Arg Met Met Ser Gly Arg
            740                 745                 750
Pro Ala Met Asp Ile Pro Pro Ile His Pro Gly Met Ile Pro Pro Lys
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        755                 760                 765
Pro Leu Met Arg Arg Asp Gln Met Glu Gly Ser Pro Asn Ser Ser Glu
    770                 775                 780
Ser Phe Glu His Ile Ala Arg Ser Ala Arg Asp His Ala Ile Ser Leu
785                 790                 795                 800
Ser Glu Pro Arg Met Leu Trp Gly Ser Asp Pro Tyr Pro His Ala Glu
                805                 810                 815
Pro Gln Gln Ala Thr Thr Pro Lys Ala Thr Glu Glu Pro Glu Asp Val
            820                 825                 830
Arg Ser Glu Ala Ala Leu Asp Gln Glu Gln Ile Thr Ala Ala Tyr Ser
        835                 840                 845
Val Glu His Asn Gln Leu Glu Ala His Pro Lys Ala Asp Phe Ile Arg
    850                 855                 860
Glu Ser Ser Glu Ala Gln Val Gln Lys Phe Leu Ser Arg Ser Val Glu
865                 870                 875                 880
Asp Val Arg Pro His His Thr Asp Ala Asn Asn Gln Ser Ala Cys Phe
                885                 890                 895
Glu Ala Pro Asp Gln Lys Thr Leu Ser Ala Pro Gln Glu Glu Arg Ile
            900                 905                 910
Ser Ala Val Glu Ser Gln Pro Ser Arg Lys Arg Ser Val Ser His Gly
        915                 920                 925
Ser Asn His Thr Gln Lys Pro Asp Glu Gln Arg Ser Glu Pro Ser Ala
    930                 935                 940
Gly Ile Pro Lys Val Thr Ser Arg Cys Ile Asp Ser Lys Glu Pro Ile
945                 950                 955                 960
Glu Arg Pro Glu Glu Lys Pro Lys Lys Glu Gly Phe Ile Arg Ser Ser
                965                 970                 975
Glu Gly Pro Lys Pro Glu Lys Val Tyr Lys Ser Lys Ser Glu Thr Arg
            980                 985                 990
Trp Gly Pro Arg Pro Ser Ser Asn Arg Arg Glu Glu Val Asn Asp Arg
        995                 1000                1005
Pro Val Arg Arg Ser Gly Pro Ile Lys Lys Pro Val Leu Arg Asp Met
    1010                1015                1020
Lys Glu Glu Arg Glu Gln Arg Lys Glu Lys Glu Gly Glu Lys Ala Glu
1025                1030                1035                1040
Lys Val Thr Glu Lys Val Val Val Lys Pro Glu Lys Thr Glu Lys Lys
                1045                1050                1055
Asp Leu Pro Pro Pro Pro Pro Pro Pro Gln Pro Pro Ala Pro Ile Gln
            1060                1065                1070
Pro Gln Ser Val Pro Pro Pro Ile Gln Pro Glu Ala Glu Lys Phe Pro
        1075                1080                1085
Ser Thr Glu Thr Ala Thr Leu Ala Gln Lys Pro Ser Gln Asp Thr Glu
    1090                1095                1100
Lys Pro Leu Glu Pro Val Ser Thr Val Gln Val Glu Pro Ala Val Lys
1105                1110                1115                1120
Thr Val Asn Gln Gln Thr Met Ala Ala Pro Val Val Lys Glu Glu Lys
                1125                1130                1135
Gln Pro Glu Lys Val Ile Ser Lys Asp Leu Val Ile Glu Arg Pro Arg
            1140                1145                1150
Pro Asp Ser Arg Pro Ala Val Lys Lys Glu Ser Thr Leu Pro Pro Arg
        1155                1160                1165
Thr Tyr Trp Lys Glu Ala Arg Glu Arg Asp Trp Phe Pro Asp Gln Gly
    1170                1175                1180
Tyr Arg Gly Arg Gly Arg Gly Glu Tyr Tyr Ser Arg Gly Arg Ser Tyr
1185                1190                1195                1200
Arg Gly Ser Tyr Gly Gly Arg Gly Arg Gly Gly Arg Gly His Thr Arg
                1205                1210                1215
Asp Tyr Pro Gln Tyr Arg Asp Asn Lys Pro Arg Ala Glu His Ile Pro
            1220                1225                1230
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1235 1240 1245
Ser Asp Phe Glu Val Val Pro Lys Arg Arg Arg Gln Arg Gly Ser Glu
1250 1255 1260
Thr Asp Thr Asp Ser Glu Ile His Glu Ser Ala Ser Asp Lys Asp Ser
1265 1270 1275 1280
Leu Ser Lys Gly Lys Leu Pro Lys Arg Glu Glu Arg Pro Glu Asn Lys
1285 1290 1295
Lys Pro Val Lys Pro His Ser Ser Phe Lys Pro Asp Asn His Val Arg
1300 1305 1310
Ile Asp Asn Arg Leu Leu Glu Lys Pro Tyr Val Arg Asp Asp Asp Lys
1315 1320 1325
Ala Lys Pro Gly Phe Leu Pro Lys Gly Glu Pro Thr Arg Arg Gly Arg
1330 1335 1340
Gly Gly Thr Phe Arg Arg Gly Gly Arg Asp Pro Gly Gly Arg Pro Ser
1345 1350 1355 1360
Arg Pro Ser Thr Leu Arg Arg Pro Ala Tyr Arg Asp Asn Gln Trp Asn
1365 1370 1375
Pro Arg Gln Ser Glu Val Pro Lys Pro Glu Asp Gly Glu Pro Pro Arg
1380 1385 1390
Arg His Glu Gln Phe Ile Pro Ile Ala Ala Asp Lys Arg Pro Pro Lys
1395 1400 1405
Phe Glu Arg Lys Phe Asp Pro Ala Arg Glu Arg Pro Arg Arg Gln Arg
1410 1415 1420
Pro Thr Arg Pro Pro Arg Gln Asp Lys Pro Pro Arg Phe Arg Arg Leu
1425 1430 1435 1440
Arg Glu Arg Glu Ala Ala Ser Lys Ser Asn Glu Val Val Ala Val Pro
1445 1450 1455
Thr Asn Gly Thr Val Asn Asn Val Ala Gln Glu Pro Val Asn Thr Leu
1460 1465 1470
Gly Asp Ile Ser Gly Asn Lys Thr Pro Asp Leu Ser Asn Gln Asn Ser
1475 1480 1485
Ser Asp Gln Ala Asn Glu Glu Trp Glu Thr Ala Ser Glu Ser Ser Asp
1490 1495 1500
Phe Asn Glu Arg Arg Glu Arg Asp Glu Lys Lys Asn Ala Asp Leu Asn
1505 1510 1515 1520
Ala Gln Thr Val Val Lys Val Gly Glu Asn Val Leu Pro Pro Lys Arg
1525 1530 1535
Glu Ile Ala Lys Arg Ser Phe Ser Ser Gln Arg Pro Val Asp Arg Gln
1540 1545 1550
Asn Arg Arg Gly Asn Asn Gly Pro Pro Lys Ser Gly Arg Asn Phe Ser
1555 1560 1565
Gly Pro Arg Asn Glu Arg Arg Ser Gly Pro Pro Ser Lys Ser Gly Lys
1570 1575 1580
Arg Gly Pro Phe Asp Asp Gln Pro Ala Gly Thr Thr Gly Val Asp Leu
1585 1590 1595 1600
Ile Asn Gly Ser Ser Ala His His Gln Glu Gly Val Pro Asn Gly Thr
1605 1610 1615
Gly Gln Lys Asn Ser Lys Asp Ser Thr Gly Lys Lys Arg Glu Asp Pro
1620 1625 1630
Lys Pro Gly Pro Lys Lys Pro Lys Glu Lys Val Asp Ala Leu Ser Gln
1635 1640 1645
Phe Asp Leu Asn Asn Tyr Ala Ser Val Val Ile Ile Asp Asp His Pro
1650 1655 1660
Glu Val Thr Val Ile Glu Asp Pro Gln Ser Asn Leu Asn Asp Asp Gly
1665 1670 1675 1680
Phe Thr Glu Val Val Ser Lys Lys Gln Gln Lys Arg Leu Gln Asp Glu
1685 1690 1695
Glu Arg Arg Lys Lys Glu Glu Gln Val Ile Gln Val Trp Asn Lys Lys

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            1700                 1705                 1710
Asn Ala Asn Glu Lys Gly Arg Ser Gln Thr Ser Lys Leu Pro Pro Arg
        1715                 1720                 1725
Phe Ala Lys Lys Gln Ala Thr Gly Ile Gln Gln Ala Gln Ser Ser Ala
    1730                 1735                 1740
Ser Val Pro Pro Leu Ala Ser Ala Pro Leu Pro Pro Ser Thr Ser Ala
1745                 1750                 1755                 1760
Ser Val Pro Ala Ser Thr Ser Ala Pro Leu Pro Ala Thr Leu Thr Pro
                1765                 1770                 1775
Val Pro Ala Ser Thr Ser Ala Pro Val Pro Ala Ser Thr Leu Ala Pro
            1780                 1785                 1790
Val Leu Ala Ser Thr Ser Ala Pro Val Pro Ala Ser Pro Leu Ala Pro
        1795                 1800                 1805
Val Ser Ala Ser Ala Ser Val Ser Ala Ser Val Pro Ala Ser Thr Ser
    1810                 1815                 1820
Ala Ala Ala Ile Thr Ser Ser Ser Ala Pro Ala Ser Ala Pro Ala Pro
1825                 1830                 1835                 1840
Thr Pro Ile Leu Ala Ser Val Ser Thr Pro Ala Ser Val Thr Ile Leu
                1845                 1850                 1855
Ala Ser Ala Ser Ile Pro Ile Leu Ala Ser Ala Leu Ala Ser Thr Ser
            1860                 1865                 1870
Ala Pro Thr Pro Ala Pro Ala Ala Ser Ser Pro Ala Ala Pro Val Ile
        1875                 1880                 1885
Thr Ala Pro Thr Ile Pro Ala Ser Ala Pro Thr Ala Ser Val Pro Leu
    1890                 1895                 1900
Ala Pro Ala Ser Ala Ser Ala Pro Ala Pro Ala Pro Thr Pro Val Ser
1905                 1910                 1915                 1920
Ala Pro Asn Pro Ala Pro Pro Ala Pro Ala Gln Thr Gln Ala Gln Thr
                1925                 1930                 1935
His Lys Pro Val Gln Asn Pro Leu Gln Thr Thr Ser Gln Ser Ser Lys
            1940                 1945                 1950
Gln Pro Pro Pro Ser Ile Arg Leu Pro Ser Ala Gln Thr Pro Asn Gly
        1955                 1960                 1965
Thr Asp Tyr Val Ala Ser Gly Lys Ser Ile Gln Thr Pro Gln Ser His
    1970                 1975                 1980
Gly Thr Leu Thr Ala Glu Leu Trp Asp Asn Lys Val Ala Pro Pro Ala
1985                 1990                 1995                 2000
Val Leu Asn Asp Ile Ser Lys Lys Leu Gly Pro Ile Ser Pro Pro Gln
                2005                 2010                 2015
Pro Pro Ser Val Ser Ala Trp Asn Lys Pro Leu Thr Ser Phe Gly Ser
            2020                 2025                 2030
Ala Pro Ser Ser Glu Gly Ala Lys Asn Gly Gln Glu Ser Gly Leu Glu
        2035                 2040                 2045
Ile Gly Thr Asp Thr Ile Gln Phe Gly Ala Pro Ala Ser Asn Gly Asn
    2050                 2055                 2060
Glu Asn Glu Val Val Pro Val Leu Ser Glu Lys Ser Ala Asp Lys Ile
2065                 2070                 2075                 2080
Pro Glu Pro Lys Glu Gln Arg Gln Lys Gln Pro Arg Ala Gly Pro Ile
                2085                 2090                 2095
Lys Ala Gln Lys Leu Pro Asp Leu Ser Pro Val Glu Asn Lys Glu His
            2100                 2105                 2110
Lys Pro Gly Pro Ile Gly Lys Glu Arg Ser Leu Lys Asn Arg Lys Val
        2115                 2120                 2125
Lys Asp Ala Gln Gln Val Glu Pro Glu Gly Gln Glu Lys Pro Ser Pro
    2130                 2135                 2140
Ala Thr Val Arg Ser Thr Asp Pro Val Thr Thr Lys Glu Thr Lys Ala
2145                 2150                 2155                 2160
Val Ser Glu Met Ser Thr Glu Ile Gly Thr Met Ile Ser Val Ser Ser
                2165                 2170                 2175
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Ala Glu Tyr Gly Thr Asn Ala Lys Glu Ser Val Thr Asp Tyr Thr Thr
2180 2185 2190
Pro Ser Ser Ser Leu Pro Asn Thr Val Ala Thr Asn Asn Thr Lys Met
2195 2200 2205
Glu Asp Thr Leu Val Asn Asn Val Pro Leu Pro Asn Thr Leu Pro Leu
2210 2215 2220
Pro Lys Arg Glu Thr Ile Gln Gln Ser Ser Ser Leu Thr Ser Val Pro
2225 2230 2235 2240
Pro Thr Thr Phe Ser Leu Thr Phe Lys Met Glu Ser Ala Arg Lys Ala
2245 2250 2255
Trp Glu Asn Ser Pro Asn Val Arg Glu Lys Gly Ser Pro Val Thr Ser
2260 2265 2270
Thr Ala Pro Pro Ile Ala Thr Gly Val Ser Ser Ser Ala Ser Gly Pro
2275 2280 2285
Ser Thr Ala Asn Tyr Asn Ser Phe Ser Ser Ala Ser Met Pro Gln Ile
2290 2295 2300
Pro Val Ala Ser Val Thr Pro Thr Ala Ser Leu Ser Gly Ala Gly Thr
2305 2310 2315 2320
Tyr Thr Thr Ser Ser Leu Ser Thr Lys Ser Thr Thr Thr Ser Asp Pro
2325 2330 2335
Pro Asn Ile Cys Lys Val Lys Pro Gln Gln Leu Gln Thr Ser Ser Leu
2340 2345 2350
Pro Ser Ala Ser His Phe Ser Gln Leu Ser Cys Met Pro Ser Leu Ile
2355 2360 2365
Ala Gln Gln Gln Gln Asn Pro Gln Val Tyr Val Ser Gln Ser Ala Ala
2370 2375 2380
Ala Gln Ile Pro Ala Phe Tyr Met Asp Thr Ser His Leu Phe Asn Thr
2385 2390 2395 2400
Gln His Ala Arg Leu Ala Pro Pro Ser Leu Ala Gln Gln Gln Gly Phe
2405 2410 2415
Gln Pro Gly Leu Ser Gln Pro Thr Ser Val Gln Gln Ile Pro Ile Pro
2420 2425 2430
Ile Tyr Ala Pro Leu Gln Gly Gln His Gln Ala Gln Leu Ser Leu Gly
2435 2440 2445
Ala Gly Pro Ala Val Ser Gln Ala Gln Glu Leu Phe Ser Ser Ser Leu
2450 2455 2460
Gln Pro Tyr Arg Ser Gln Pro Ala Phe Met Gln Ser Ser Leu Ser Gln
2465 2470 2475 2480
Pro Ser Val Val Leu Ser Gly Thr Ala Ile His Asn Phe Pro Thr Val
2485 2490 2495
Gln His Gln Glu Leu Ala Lys Ala Gln Ser Gly Leu Ala Phe Gln Gln
2500 2505 2510
Thr Ser Asn Thr Gln Pro Ile Pro Ile Leu Tyr Glu His Gln Leu Gly
2515 2520 2525
Gln Ala Ser Gly Leu Gly Gly Ser Gln Leu Ile Asp Thr His Leu Leu
2530 2535 2540
Gln Ala Arg Ala Asn Leu Thr Gln Ala Ser Asn Leu Tyr Ser Gly Gln
2545 2550 2555 2560
Val Gln Gln Pro Gly Gln Thr Asn Phe Tyr Asn Thr Ala Gln Ser Pro
2565 2570 2575
Ser Ala Leu Gln Gln Val Thr Val Pro Leu Pro Ala Ser Gln Leu Ser
2580 2585 2590
Leu Pro Asn Phe Gly Ser Thr Gly Gln Pro Leu Ile Ala Leu Pro Gln
2595 2600 2605
Thr Leu Gln Pro Pro Leu Gln His Thr Thr Pro Gln Ala Gln Ala Gln
2610 2615 2620
Ser Leu Ser Arg Pro Ala Gln Val Ser Gln Pro Phe Arg Gly Leu Ile
2625 2630 2635 2640
Pro Ala Gly Thr Gln His Ser Met Ile Ala Thr Thr Gly Lys Met Ser

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            2645                2650                2655
Glu Met Glu Leu Lys Ala Phe Gly Ser Gly Ile Asp Ile Lys Pro Gly
        2660                2665                2670
Thr Pro Pro Ile Ala Gly Arg Ser Thr Thr Pro Thr Ser Ser Pro Ser
    2675                2680                2685
Gly Leu Leu Leu Gln Val Arg Thr Ala Ser Pro Ala Lys
2690                2695                2700
```

<210> 84
<211> 597
<212> DNA
<213> Homo sapiens

<400> 84

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ggctctgccg tagttttgcc cctggccagg attgctacag ttgtgattgg aggagttgtg 180
gccatggcgg ctgtgcccat ggtgctcagt gccatgggct tcactgcggc gggaatcgcc 240
tcgtcctcca tagcagccaa gatgatgtcc gcggcggcca ttgccaatgg gggtggagtt 300
gcctcgggca gccttgtggg tactctgcag tcactgggag caactggact ctccggattg 360
accaagttca tcctgggctc cattgggtct gccattgcgg ctgtcattgc gaggttctac 420
tagctccctg cccctcgccc tgcagagaag agaaccatgc caggggagaa ggcacccagc 480
catcctgacc cagcgaggag ccaactatcc caaatatacc tgggtgaaat ataccaaatt 540
ctgcatctcc agaggaaaat aagaaataaa gatgaattgt tgcaactctt aaaaaaa    597
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<210> 85
<211> 122
<212> PRT
<213> Homo sapiens

<400> 85

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Met Glu Ala Ser Ala Leu Thr Ser Ser Ala Val Thr Ser Val Ala Lys
1               5                   10                  15
Val Val Arg Val Ala Ser Gly Ser Ala Val Val Leu Pro Leu Ala Arg
            20                  25                  30
Ile Ala Thr Val Val Ile Gly Gly Val Val Ala Met Ala Ala Val Pro
        35                  40                  45
Met Val Leu Ser Ala Met Gly Phe Thr Ala Ala Gly Ile Ala Ser Ser
    50                  55                  60
Ser Ile Ala Ala Lys Met Met Ser Ala Ala Ala Ile Ala Asn Gly Gly
65                  70                  75                  80
Gly Val Ala Ser Gly Ser Leu Val Gly Thr Leu Gln Ser Leu Gly Ala
                85                  90                  95
Thr Gly Leu Ser Gly Leu Thr Lys Phe Ile Leu Gly Ser Ile Gly Ser
            100                 105                 110
Ala Ile Ala Ala Val Ile Ala Arg Phe Tyr
        115                 120
```

<210> 86
<211> 1032
<212> DNA
<213> Homo sapiens

<400> 86

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ggagggtggg cagcactcgc tttattgtcc agcattccac atggatagtc gccacacctt 60
tgcccctgct gcgatgaccc tgtcgccact tctgctgttc ctgccaccgc tgctgctgct 120
gctggacgtc cccacggcgg cggtgcaggc gtcccctctg caagcgttag acttctttgg 180
```

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gaatgggcca ccagttaact acaagacagg caatctatac ctgcgggggc ccctgaagaa 240
gtccaatgca ccgcttgtca atgtgaccct ctactatgaa gcactgtgcg gtggctgccg 300
agccttcctg atccgggagc tcttcccaac atggctgttg gtcatggaga tcctcaatgt 360
cacgtcggtg ccctacggaa acgcacagga acaaaatgtc agtggcaggt gggagttcaa 420
gtgccagctt ggagaagagg agtgcaaatt caacaaggtg gaggcctgcg tgttggatga 480
acttgacatg gagctagcct tcctgaccat gtctggcatg gcatggaaga gtttgaggac 540
atggagagaa gtctgccact atgcctgcag ctctacgccc cagggctgtc gccagaacta 600
tcatggagtg tgcaatgggg gaccgcggca tgcagctcat gcacgccaac gcccagcgga 660
cagatgctct ccagccaccg cacgagtatg tgccctgggt caccgtcaat gggaaaccct 720
tggaagatca gacccagctc cttacccttg tctgccagtt gtaccagggc aagaagccgg 780
atgtctgccc ttcctcaacc agctccctcc ggagtgtttg cttcgagtgt tggccggtgg 840
gctgcggaga gctcatggaa ggcgagtggg aactcggctg cctgcctttt tttctgatcc 900
agaccctcgg cacctgctac ttaccaactg gaaaatttta tgcatcccat gaagcccaga 960
tacacaaaat tccaccccta gatcaagaat cctgctccac taagaatggt gctaaagtaa 1020
aactagttta at                                                     1032
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<210> 87
<211> 303
<212> PRT
<213> Homo sapiens

<400> 87

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Met Asp Ser Arg His Thr Phe Ala Pro Ala Ala Met Thr Leu Ser Pro
 1               5                  10                  15
Leu Leu Leu Phe Leu Pro Pro Leu Leu Leu Leu Leu Asp Val Pro Thr
            20                  25                  30
Ala Ala Val Gln Ala Ser Pro Leu Gln Ala Leu Asp Phe Phe Gly Asn
        35                  40                  45
Gly Pro Pro Val Asn Tyr Lys Thr Gly Asn Leu Tyr Leu Arg Gly Pro
    50                  55                  60
Leu Lys Lys Ser Asn Ala Pro Leu Val Asn Val Thr Leu Tyr Tyr Glu
65                  70                  75                  80
Ala Leu Cys Gly Gly Cys Arg Ala Phe Leu Ile Arg Glu Leu Phe Pro
                85                  90                  95
Thr Trp Leu Leu Val Met Glu Ile Leu Asn Val Thr Ser Val Pro Tyr
            100                 105                 110
Gly Asn Ala Gln Glu Gln Asn Val Ser Gly Arg Trp Glu Phe Lys Cys
        115                 120                 125
Gln Leu Gly Glu Glu Glu Cys Lys Phe Asn Lys Val Glu Ala Cys Val
    130                 135                 140
Leu Asp Glu Leu Asp Met Glu Leu Ala Phe Leu Thr Met Ser Gly Met
145                 150                 155                 160
Ala Trp Lys Ser Leu Arg Thr Trp Arg Glu Val Cys His Tyr Ala Cys
                165                 170                 175
Ser Ser Thr Pro Gln Gly Cys Arg Gln Asn Tyr His Gly Val Cys Asn
            180                 185                 190
Gly Gly Pro Arg His Ala Ala His Ala Arg Gln Arg Pro Ala Asp Arg
        195                 200                 205
Cys Ser Pro Ala Thr Ala Arg Val Cys Ala Leu Gly His Arg Gln Trp
    210                 215                 220
Glu Thr Leu Gly Arg Ser Asp Pro Ala Pro Tyr Pro Cys Leu Pro Val
225                 230                 235                 240
Val Pro Gly Gln Glu Ala Gly Cys Leu Pro Phe Leu Asn Gln Leu Pro
                245                 250                 255
Pro Glu Cys Leu Leu Arg Val Leu Ala Gly Gly Leu Arg Arg Ala His
            260                 265                 270
Gly Arg Arg Val Gly Thr Arg Leu Pro Ala Phe Phe Ser Asp Pro Asp
        275                 280                 285
Pro Arg His Leu Leu Leu Thr Asn Trp Lys Ile Leu Cys Ile Pro
```

290 295 300

<210> 88
<211> 905
<212> DNA
<213> Homo sapiens

<400> 88
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tgggctctag agaggaagcc cctctgagcc ctcagcccct ctttcctccc tctcctaaag 120
taatttgatc ctcaggaatt tgttctgccc tcatctggcc ctggccagct ctgcatttga 180
caaatgccag gaagaggaaa ctgttgagaa aacggaacta ctggggaaag ggagggctca 240
ctgagaacca tcccggtaac ccgaccgccg ctggtcacca tgaaccacat tgtgcaaacc 300
ttctctcctg tcaacagcgg ccagcctccc aactacgaga tgctcaagga ggagcaggaa 360
gtggctatgc tggggggcc ccacaaccct gctcccccga cgtccaccgt gatccacatc 420
cgcagcgaga cctccgtgcc tgaccatgtc gtctggtccc tgttcaacac cctcttcatg 480
aacacctgct gcctgggctt catagcattc gcctactccg tgaagtctag ggacaggaag 540
atggttggcg acgtgaccgg ggcccaggcc tatgcctcca ccgccaagtg cctgaacatc 600
tgggccctga ttttgggcat cttcatgacc attctgctcg tcatcatccc agtgttggtc 660
gtccaggccc agcgatagat caggaggcat cattgaggcc aggagctctg cccgtgacct 720
gtatcccacg tactctatct tccattcctc gccctgcccc cagaggccag gagctctgcc 780
cttgacctgt attccactta ctccaccttc cattcctcgc cctgtcccca cagccgagtc 840
ctgcatcagc cctttatcct cacacgcttt tctacaatgg cattcaataa agtgtatatg 900
tttct 905

<210> 89
<211> 132
<212> PRT
<213> Homo sapiens

<400> 89
Met Asn His Ile Val Gln Thr Phe Ser Pro Val Asn Ser Gly Gln Pro
1 5 10 15
Pro Asn Tyr Glu Met Leu Lys Glu Glu Gln Glu Val Ala Met Leu Gly
20 25 30
Gly Pro His Asn Pro Ala Pro Pro Thr Ser Thr Val Ile His Ile Arg
35 40 45
Ser Glu Thr Ser Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr
50 55 60
Leu Phe Met Asn Thr Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser
65 70 75 80
Val Lys Ser Arg Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln
85 90 95
Ala Tyr Ala Ser Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu
100 105 110
Gly Ile Phe Met Thr Ile Leu Leu Val Ile Ile Pro Val Leu Val Val
115 120 125
Gln Ala Gln Arg
130

<210> 90
<211> 2499
<212> DNA
<213> Homo sapiens

<400> 90
agatgcgagc actgcggctg ggcgctgagg atcagccgct tcctgcctgg attccacagc 60

ttcgcgccgt gtactgtcgc cccatccctg cgcgcccagc ctgccaagca gcgtgccccg 120
gttgcaggcg tcatgcagcg ggcgcgaccc acgctctggg ccgctgcgct gactctgctg 180
gtgctgctcc gcgggccgcc ggtggcgcgg gctggcgcga gctcgggggg cttgggtccc 240
gtggtgcgct gcgagccgtg cgacgcgcgt gcactggccc agtgcgcgcc tccgcccgcc 300
gtgtgcgcgg agctggtgcg cgagccgggc tgcggctgct gcctgacgtg cgcactgagc 360
gagggccagc cgtgcggcat ctacaccgag cgctgtggct ccggccttcg ctgccagccg 420
tcgcccgacg aggcgcgacc gctgcaggcg ctgctggacg gccgcgggct ctgcgtcaac 480
gctagtgccg tcagccgcct gcgcgcctac ctgctgccag cgccgccagc tccaggaaat 540
gctagtgagt cggaggaaga ccgcagcgcc ggcagtgtgg agagcccgtc cgtctccagc 600
acgcaccggg tgtctgatcc caagttccac cccctccatt caaagataat catcatcaag 660
aaagggcatg ctaaagacag ccagcgctac aaagttgact acgagtctca gagcacagat 720
acccagaact tctcctccga gtccaagcgg gagacagaat atggtccctg ccgtagagaa 780
atggaagaca cactgaatca cctgaagttc ctcaatgtgc tgagtcccag gggtgtacac 840
attcccaact gtgacaagaa gggattttat aagaaaaagc agtgtcgccc ttccaaaggc 900
aggaagcggg gcttctgctg gtgtgtggat aagtatgggc agcctctccc aggctacacc 960
accaagggga aggaggacgt gcactgctac agcatgcaga gcaagtagac gcctgccgca 1020
aggttaatgt ggagctcaaa tatgccttat tttctacaaa agactgccaa ggacatgacc 1080
agcagctggc tacagcctcg atttatattt ctgtttgtgg tgaactgatt ttttttaaac 1140
caaagtttag aaagaggttt ttgaaatgcc tatggtttct ttgaatggta aacttgagca 1200
tcttttcact ttccagtagt cagcaaagag cagtttgaat ttcttgtcg cttcctatca 1260
aaatatctag agactcgagc acagcaccca gacttcatgc gcccgtggaa tgctcaccac 1320
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gagaacacgc ttcacccccca ctccctgtac agtgcgcaca ggctttatcg agaataggaa 1440
aacctttaaa ccccggtcat ccggacatcc caacgcatgc tcctggagct cacagccttc 1500
tgtggtgtca tttctgaaac aagggcgtgg atccctcaac ccagaagagt gtttatgtct 1560
tcaagtgacc tgtactgctt ggggactatt tgagaaaata aggtggagtc ctacttgttt 1620
cacaaatatg tatctaagaa tgttctaggg cactctggga acctataaag gcaggtattt 1680
cgggccctcc tcttcaggaa tcttcctgaa gacatggccc agtcgaaggc ccaggatggc 1740
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tcagaggcat cacaagtaat ggcacaattc ttcggatgac tgcagaaaat agtgttttgt 1860
agttcaacaa ctcaagacga agcttatttc tgaggataag ctctttaaag acaaagcttt 1920
attttcatct ctcatctttt gtcctcctta gcacaatgca aaaaagaata gtaatatcag 1980
aacaggaagg aggaatggct tgctggggag cccatccagg acactgggag cacatagaga 2040
ttcacccatg tttgttgaac ttagagtcat tctcatgctt ttctttataa ttcacacata 2100
tatgcagaga agatatgttc ttgttaacat tgtatacaac atagccccaa atatagtaag 2160
atctatacta gataatccta gatgaaatgt tagagatgct atatgataca actgtggcca 2220
tgactgagga aaggagctca cgcccagaga ctgggctgct ctcccggagg ccaaacccaa 2280
gaaggtctgg caaagtcagg ctcagggaga ctctgccctg ctgcagacct cggtgtggac 2340
acacgctgca tagagctctc cttgaaaaca gaggggtctc aagacattct gcctacctat 2400
tagcttttct ttattttttt aactttttgg ggggaaaagt atttttgaga agtttgtctt 2460
gcaatgtatt tataaatagt aaataaagtt tttaccatt 2499

<210> 91
<211> 291
<212> PRT
<213> Homo sapiens

<400> 91
Met Gln Arg Ala Arg Pro Thr Leu Trp Ala Ala Ala Leu Thr Leu Leu
1 5 10 15
Val Leu Leu Arg Gly Pro Pro Val Ala Arg Ala Gly Ala Ser Ser Gly
20 25 30
Gly Leu Gly Pro Val Val Arg Cys Glu Pro Cys Asp Ala Arg Ala Leu
35 40 45
Ala Gln Cys Ala Pro Pro Pro Ala Val Cys Ala Glu Leu Val Arg Glu
50 55 60
Pro Gly Cys Gly Cys Cys Leu Thr Cys Ala Leu Ser Glu Gly Gln Pro
65 70 75 80
Cys Gly Ile Tyr Thr Glu Arg Cys Gly Ser Gly Leu Arg Cys Gln Pro

```
                85                  90                  95
Ser Pro Asp Glu Ala Arg Pro Leu Gln Ala Leu Leu Asp Gly Arg Gly
            100                 105                 110
Leu Cys Val Asn Ala Ser Ala Val Ser Arg Leu Arg Ala Tyr Leu Leu
        115                 120                 125
Pro Ala Pro Pro Ala Pro Gly Asn Ala Ser Glu Ser Glu Glu Asp Arg
    130                 135                 140
Ser Ala Gly Ser Val Glu Ser Pro Ser Val Ser Ser Thr His Arg Val
145                 150                 155                 160
Ser Asp Pro Lys Phe His Pro Leu His Ser Lys Ile Ile Ile Ile Lys
                165                 170                 175
Lys Gly His Ala Lys Asp Ser Gln Arg Tyr Lys Val Asp Tyr Glu Ser
            180                 185                 190
Gln Ser Thr Asp Thr Gln Asn Phe Ser Ser Glu Ser Lys Arg Glu Thr
        195                 200                 205
Glu Tyr Gly Pro Cys Arg Arg Glu Met Glu Asp Thr Leu Asn His Leu
    210                 215                 220
Lys Phe Leu Asn Val Leu Ser Pro Arg Gly Val His Ile Pro Asn Cys
225                 230                 235                 240
Asp Lys Lys Gly Phe Tyr Lys Lys Lys Gln Cys Arg Pro Ser Lys Gly
                245                 250                 255
Arg Lys Arg Gly Phe Cys Trp Cys Val Asp Lys Tyr Gly Gln Pro Leu
            260                 265                 270
Pro Gly Tyr Thr Thr Lys Gly Lys Glu Asp Val His Cys Tyr Ser Met
        275                 280                 285
Gln Ser Lys
    290


<210> 92
<211> 1639
<212> DNA
<213> Homo sapiens

<400> 92
agcagagcac acaagcttct aggacaagag ccaggaagaa accaccggaa ggaaccatct 60
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ctgcagctct gtgtgaaggt gcagttttgc caaggagtgc taaagaactt agatgtcagt 180
gcataaagac atactccaaa cctttccacc ccaaatttat caaagaactg agagtgattg 240
agagtggacc acactgcgcc aacacagaaa ttattgtaaa gctttctgat ggaagagagc 300
tctgtctgga ccccaaggaa aactgggtgc agagggttgt ggagaagttt ttgaagaggg 360
ctgagaattc ataaaaaaat tcattctctg tggtatccaa gaatcagtga agatgccagt 420
gaaacttcaa gcaaatctac ttcaacactt catgtattgt gtgggtctgt tgtagggttg 480
ccagatgcaa tacaagattc ctggttaaat ttgaatttca gtaaacaatg aatagttttt 540
cattgtacca tgaaatatcc agaacatact tatatgtaaa gtattattta tttgaatcta 600
caaaaaacaa caaataattt ttaaatataa ggatttcct agatattgca cgggagaata 660
tacaaatagc aaaattgagc caagggccaa gagaatatcc gaactttaat ttcaggaatt 720
gaatgggttt gctagaatgt gatatttgaa gcatcacata aaaatgatgg gacaataaat 780
tttgccataa agtcaaattt agctggaaat cctggatttt tttctgttaa atctggcaac 840
cctagtctgc tagccaggat ccacaagtcc ttgttccact gtgccttggt ttctccttta 900
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ctatttatta tttatgtatt tatttaagca tcaaatattt gtgcaagaat ttggaaaaat 1080
agaagatgaa tcattgattg aatagttata aagatgttat agtaaattta ttttatttta 1140
gatattaaat gatgttttat tagataaatt tcaatcaggg tttttagatt aaacaaagaa 1200
acaattgggt acccagttaa attttcattt cagataaaca acaaataatt ttttagtata 1260
agtacattat tgtttatctg aaagttttaa ttgaactaac aatcctagtt tgatactccc 1320
agtcttgtca ttgccagctg tgttggtagt gctgtgttga attacggaat aatgagttag 1380
aactattaaa acagccaaaa ctccacagtc aatattagta atttcttgct ggttgaaact 1440
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tgtttattat gtacaaatag attcttataa tattatttaa atgactgcat ttttaaatac 1500
aaggctttat atttttaact ttaagatgtt tttatgtgct ctccaaattt tttttactgt 1560
ttctgattgt atggaaatat aaaagtaaat atgaaacatt taaaatataa tttgttgtca 1620
aagtaaaaaa aaaaaaaaa 1639

<210> 93
<211> 99
<212> PRT
<213> Homo sapiens

<400> 93
Met Thr Ser Lys Leu Ala Val Ala Leu Leu Ala Ala Phe Leu Ile Ser
1 5 10 15
Ala Ala Leu Cys Glu Gly Ala Val Leu Pro Arg Ser Ala Lys Glu Leu
20 25 30
Arg Cys Gln Cys Ile Lys Thr Tyr Ser Lys Pro Phe His Pro Lys Phe
35 40 45
Ile Lys Glu Leu Arg Val Ile Glu Ser Gly Pro His Cys Ala Asn Thr
50 55 60
Glu Ile Ile Val Lys Leu Ser Asp Gly Arg Glu Leu Cys Leu Asp Pro
65 70 75 80
Lys Glu Asn Trp Val Gln Arg Val Val Glu Lys Phe Leu Lys Arg Ala
85 90 95
Glu Asn Ser

<210> 94
<211> 1840
<212> DNA
<213> Homo sapiens

<400> 94
tccacacaca caaaaaacct gcgcgtgagg ggggaggaaa agcagggcct ttaaaaaggc 60
aatcacaaca acttttgctg ccaggatgcc cttgctttgg ctgagaggat ttctgttggc 120
aagttgctgg attatagtga ggagttcccc caccccagga tccgaggggc acagcgcggc 180
ccccgactgt ccgtcctgtg cgctggccgc cctcccaaag gatgtaccca actctcagcc 240
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cgatgtcacc cagccggtac ccaaggcggc gcttctgaac gcgatcagaa agcttcatgt 360
gggcaaagtc ggggagaacg ggtatgtgga gatagaggat gacattggaa ggagggcaga 420
aatgaatgaa cttatggagc agacctcgga gatcatcacg tttgccgagt caggaacagc 480
caggaagacg ctgcacttcg agatttccaa ggaaggcagt gacctgtcag tggtggagcg 540
tgcagaagtc tggctcttcc taaaagtccc caaggccaac aggaccagga ccaaagtcac 600
catccgcctc ttccagcagc agaagcaccc gcagggcagc ttggacacag gggaagaggc 660
cgaggaagtg ggcttaaagg gggagaggag tgaactgttg ctctctgaaa aagtagtaga 720
cgctcggaag agcacctggc atgtcttccc tgtctccagc agcatccagc ggttgctgga 780
ccagggcaag agctccctgg acgttcggat tgcctgtgag cagtgccagg agagtggcgc 840
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tgagtgcccg agccatatag caggcacgtc cgggtcctca ctgtccttcc actcaacagt 1200
catcaaccac taccgcatgc ggggccatag cccctttgcc aacctcaaat cgtgctgtgt 1260
gcccaccaag ctgagaccca tgtccatgtt gtactatgat gatggtcaaa acatcatcaa 1320
aaaggacatt cagaacatga tcgtggagga gtgtgggtgc tcatagagtt gcccagccca 1380
gggggaaagg gagcaagagt tgtccagaga agacagtggc aaaatgaaga aatttttaag 1440
gtttctgagt taaccagaaa aatagaaatt aaaaacaaaa caaaacaaaa aaaaaaacaa 1500
aaaaaaacaa aagtaaatta aaaacaaacc tgatgaaaca gatgaaacag atgaaggaag 1560

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atgtggaaat cttagcctgc cttagccagg gctcagagat gaagcagtga agagacagat 1620
tgggagggaa agggagaatg gtgtaccctt tatttcttct gaaatcacac tgatgacatc 1680
agttgtttaa acggggtatt gtcctttccc cccttgaggt tcccttgtga gcttgaatca 1740
accaatctga tctgcagtag tgtggactag aacaacccaa atagcatcta gaaagccatg 1800
agtttgaaag ggcccatcac aggcactttc ctagcctaat                       1840
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<210> 95
<211> 426
<212> PRT
<213> Homo sapiens

<400> 95

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Met Pro Leu Leu Trp Leu Arg Gly Phe Leu Leu Ala Ser Cys Trp Ile
 1               5                  10                  15
Ile Val Arg Ser Ser Pro Thr Pro Gly Ser Glu Gly His Ser Ala Ala
            20                  25                  30
Pro Asp Cys Pro Ser Cys Ala Leu Ala Ala Leu Pro Lys Asp Val Pro
        35                  40                  45
Asn Ser Gln Pro Glu Met Val Glu Ala Val Lys Lys His Ile Leu Asn
    50                  55                  60
Met Leu His Leu Lys Lys Arg Pro Asp Val Thr Gln Pro Val Pro Lys
65                  70                  75                  80
Ala Ala Leu Leu Asn Ala Ile Arg Lys Leu His Val Gly Lys Val Gly
                85                  90                  95
Glu Asn Gly Tyr Val Glu Ile Glu Asp Asp Ile Gly Arg Arg Ala Glu
            100                 105                 110
Met Asn Glu Leu Met Glu Gln Thr Ser Glu Ile Ile Thr Phe Ala Glu
        115                 120                 125
Ser Gly Thr Ala Arg Lys Thr Leu His Phe Glu Ile Ser Lys Glu Gly
    130                 135                 140
Ser Asp Leu Ser Val Val Glu Arg Ala Glu Val Trp Leu Phe Leu Lys
145                 150                 155                 160
Val Pro Lys Ala Asn Arg Thr Arg Thr Lys Val Thr Ile Arg Leu Phe
                165                 170                 175
Gln Gln Gln Lys His Pro Gln Gly Ser Leu Asp Thr Gly Glu Glu Ala
            180                 185                 190
Glu Glu Val Gly Leu Lys Gly Glu Arg Ser Glu Leu Leu Leu Ser Glu
        195                 200                 205
Lys Val Val Asp Ala Arg Lys Ser Thr Trp His Val Phe Pro Val Ser
    210                 215                 220
Ser Ser Ile Gln Arg Leu Leu Asp Gln Gly Lys Ser Ser Leu Asp Val
225                 230                 235                 240
Arg Ile Ala Cys Glu Gln Cys Gln Glu Ser Gly Ala Ser Leu Val Leu
                245                 250                 255
Leu Gly Lys Lys Lys Lys Lys Glu Glu Glu Gly Glu Gly Lys Lys Lys
            260                 265                 270
Gly Gly Gly Glu Gly Gly Ala Gly Ala Asp Glu Glu Lys Glu Gln Ser
        275                 280                 285
His Arg Pro Phe Leu Met Leu Gln Ala Arg Gln Ser Glu Asp His Pro
    290                 295                 300
His Arg Arg Arg Arg Arg Gly Leu Glu Cys Asp Gly Lys Val Asn Ile
305                 310                 315                 320
Cys Cys Lys Lys Gln Phe Phe Val Ser Phe Lys Asp Ile Gly Trp Asn
                325                 330                 335
Asp Trp Ile Ile Ala Pro Ser Gly Tyr His Ala Asn Tyr Cys Glu Gly
            340                 345                 350
Glu Cys Pro Ser His Ile Ala Gly Thr Ser Gly Ser Ser Leu Ser Phe
        355                 360                 365
His Ser Thr Val Ile Asn His Tyr Arg Met Arg Gly His Ser Pro Phe
```

```
    370                 375                 380
Ala Asn Leu Lys Ser Cys Cys Val Pro Thr Lys Leu Arg Pro Met Ser
385                 390                 395                 400
Met Leu Tyr Tyr Asp Asp Gly Gln Asn Ile Ile Lys Lys Asp Ile Gln
                405                 410                 415
Asn Met Ile Val Glu Glu Cys Gly Cys Ser
            420                 425


&lt;210&gt; 96
&lt;211&gt; 4637
&lt;212&gt; DNA
&lt;213&gt; Homo sapiens

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Gln Gln Arg Tyr Leu Leu Leu Ala Gly Ala Pro Arg Glu Leu Ala Val
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Pro Asp Gly Tyr Thr Asn Arg Thr Gly Ala Val Tyr Leu Cys Pro Leu
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Gln Asp Ile Ala Val Gly Ala Pro Phe Glu Gly Leu Gly Lys Val Tyr
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Ile His Gly Glu Lys Leu Gly Leu Pro Gly Leu Ala Thr Phe Gly Tyr
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Pro Gly Asp Leu Ile Asn Pro Leu Asn Leu Thr Leu Ser Asp Pro Gly
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Asp Arg Pro Ser Ser Pro Gln Arg Arg Arg Arg Gln Leu Asp Pro Gly
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Gly Gly Gln Gly Pro Pro Pro Val Thr Leu Ala Ala Ala Lys Lys Ala
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Val Lys Ala Arg Val Trp Asn Ser Thr Phe Ile Glu Asp Tyr Arg Asp
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            980                 985                 990
Trp Leu Val Leu Val Ala Val Gly Ala Gly Leu Leu Leu Leu Gly Leu
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Ile Ile Leu Leu Leu Trp Lys Cys Asp Phe Phe Lys Arg Thr Arg Tyr
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Tyr Gln Ile Met Pro Lys Tyr His Ala Val Arg Ile Arg Glu Glu Glu
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35 40 45
Phe Thr His Pro Ser Gly Val Gly Glu Arg Cys Asp Thr Pro Ala Asn
50 55 60
Leu Leu Ala Lys Gly Cys Gln Leu Asn Phe Ile Glu Asn Pro Val Ser
65 70 75 80
Gln Val Glu Ile Leu Lys Asn Lys Pro Leu Ser Val Gly Arg Gln Lys
85 90 95
Asn Ser Ser Asp Ile Val Gln Ile Ala Pro Gln Ser Leu Ile Leu Lys
100 105 110
Leu Arg Pro Gly Gly Ala Gln Thr Leu Gln Val His Val Arg Gln Thr
115 120 125
Glu Asp Tyr Pro Val Asp Leu Tyr Tyr Leu Met Asp Leu Ser Ala Ser
130 135 140
Met Asp Asp Asp Leu Asn Thr Ile Lys Glu Leu Gly Ser Arg Leu Ser
145 150 155 160
Lys Glu Met Ser Lys Leu Thr Ser Asn Phe Arg Leu Gly Phe Gly Ser
165 170 175
Phe Val Glu Lys Pro Val Ser Pro Phe Val Lys Thr Thr Pro Glu Glu
180 185 190
Ile Ala Asn Pro Cys Ser Ser Ile Pro Tyr Phe Cys Leu Pro Thr Phe
195 200 205
Gly Phe Lys His Ile Leu Pro Leu Thr Asn Asp Ala Glu Arg Phe Asn
210 215 220
Glu Ile Val Lys Asn Gln Lys Ile Ser Ala Asn Ile Asp Thr Pro Glu
225 230 235 240
Gly Gly Phe Asp Ala Ile Met Gln Ala Ala Val Cys Lys Glu Lys Ile
245 250 255
Gly Trp Arg Asn Asp Ser Leu His Leu Leu Val Phe Val Ser Asp Ala
260 265 270
Asp Ser His Phe Gly Met Asp Ser Lys Leu Ala Gly Ile Val Ile Pro
275 280 285
Asn Asp Gly Leu Cys His Leu Asp Ser Lys Asn Glu Tyr Ser Met Ser
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305 310 315 320
Gln Asn Asn Val Leu Leu Ile Phe Ala Val Thr Gln Glu Gln Val His

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Leu Gln Lys Asp Ser Gly Asn Ile Leu Gln Leu Ile Ile Ser Ala Tyr
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Glu Glu Leu Arg Ser Glu Val Glu Leu Glu Val Leu Gly Asp Thr Glu
    370                 375                 380
Gly Leu Asn Leu Ser Phe Thr Ala Ile Cys Asn Asn Gly Thr Leu Phe
385                 390                 395                 400
Gln His Gln Lys Lys Cys Ser His Met Lys Val Gly Asp Thr Ala Ser
                405                 410                 415
Phe Ser Val Thr Val Asn Ile Pro His Cys Glu Arg Arg Ser Arg His
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Ile Ile Ile Lys Pro Val Gly Leu Gly Asp Ala Leu Glu Leu Leu Val
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Ser Lys Cys His His Gly Asn Gly Ser Phe Gln Cys Gly Val Cys Ala
465                 470                 475                 480
Cys His Pro Gly His Met Gly Pro Arg Cys Glu Cys Gly Glu Asp Met
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Leu Ser Thr Asp Ser Cys Lys Glu Ala Pro Asp His Pro Ser Cys Ser
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Gly Arg Gly Asp Cys Tyr Cys Gly Gln Cys Ile Cys His Leu Ser Pro
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Tyr Gly Asn Ile Tyr Gly Pro Tyr Cys Gln Cys Asp Asn Phe Ser Cys
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Thr Thr Ser Thr Asp Ser Cys Val Ser Glu Asp Gly Val Leu Cys Ser
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Ala Ser Gly Pro Thr Cys Glu Arg Cys Pro Thr Cys Gly Asp Pro Cys
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Asn Ser Lys Arg Ser Cys Ile Glu Cys His Leu Ser Ala Ala Gly Gln
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Ala Arg Glu Glu Cys Val Asp Lys Cys Lys Leu Ala Gly Ala Thr Ile
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Gln Gly Glu Asn Glu Cys Leu Ile Thr Phe Leu Ile Thr Thr Asp Asn
        675                 680                 685
Glu Gly Lys Thr Ile Ile His Ser Ile Asn Glu Lys Asp Cys Pro Lys
    690                 695                 700
Pro Pro Asn Ile Pro Met Ile Met Leu Gly Val Ser Leu Ala Ile Leu
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Leu Ile Gly Val Val Leu Leu Cys Ile Trp Lys Leu Leu Val Ser Phe
                725                 730                 735
His Asp Arg Lys Glu Val Ala Lys Phe Glu Ala Glu Arg Ser Lys Ala
            740                 745                 750
Lys Trp Gln Thr Gly Thr Asn Pro Leu Tyr Arg Gly Ser Thr Ser Thr
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<212> DNA
<213> Homo sapiens

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35 40 45

Lys Thr Ala Val Ile Thr Val Glu Asn Gly Lys Thr Ile Gln Phe Gly
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Glu Glu Met Met Lys Arg Ala Leu Gln Tyr Ser Pro Ser Ala Gly Ile
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Pro Glu Leu Leu Ser Trp Leu Lys Gln Leu Gln Ile Lys Leu His Asn
85 90 95
Pro Pro Thr Ile His Tyr Pro Pro Ser Gln Gly Gln Met Asp Leu Cys
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Val Thr Ser Gly Ser Gln Gln Gly Leu Cys Lys Val Phe Glu Met Ile
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130 135 140
Thr Leu Gln Ser Leu His Pro Leu Gly Cys Asn Ile Ile Asn Val Ala
145 150 155 160
Ser Asp Glu Ser Gly Ile Val Pro Asp Ser Leu Arg Asp Ile Leu Ser
165 170 175
Arg Trp Lys Pro Glu Asp Ala Lys Asn Pro Gln Lys Asn Thr Pro Lys
180 185 190
Phe Leu Tyr Thr Val Pro Asn Gly Asn Asn Pro Thr Gly Asn Ser Leu
195 200 205
Thr Ser Glu Arg Lys Lys Glu Ile Tyr Glu Leu Ala Arg Lys Tyr Asp
210 215 220
Phe Leu Ile Ile Glu Asp Asp Pro Tyr Tyr Phe Leu Gln Pne Asn Lys
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Phe Arg Val Pro Thr Phe Leu Ser Met Asp Val Asp Gly Arg Val Ile
245 250 255
Arg Ala Asp Ser Phe Ser Lys Ile Ile Ser Ser Gly Leu Arg Ile Gly
260 265 270
Phe Leu Thr Gly Pro Lys Pro Leu Ile Glu Arg Val Ile Leu His Ile
275 280 285
Gln Val Ser Thr Leu His Pro Ser Thr Phe Asn Gln Leu Met Ile Ser
290 295 300
Gln Leu Leu His Glu Trp Gly Glu Glu Gly Phe Met Ala His Val Asp
305 310 315 320
Arg Val Ile Asp Phe Tyr Ser Asn Gln Lys Asp Ala Ile Leu Ala Ala
325 330 335
Ala Asp Lys Trp Leu Thr Gly Leu Ala Glu Trp His Val Pro Ala Ala
340 345 350
Gly Met Phe Leu Trp Ile Lys Val Lys Gly Ile Asn Asp Val Lys Glu
355 360 365
Leu Ile Glu Glu Lys Ala Val Lys Met Gly Val Leu Met Leu Pro Gly
370 375 380
Asn Ala Phe Tyr Val Asp Ser Ser Ala Pro Ser Pro Tyr Leu Arg Ala
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<210> 105
<211> 408
<212> PRT
<213> Homo sapiens

<400> 105

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Gly Ile Ser Leu Gln Glu Thr Thr Arg Ala Glu Thr Gly Met Ala Tyr
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Arg Asn Leu Gly Lys Ser Gly Leu Arg Val Ser Cys Leu Gly Leu Gly
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Thr Trp Val Thr Phe Gly Gly Gln Ile Ser Asp Glu Val Ala Glu Arg
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Leu Met Thr Ile Ala Tyr Glu Ser Gly Val Asn Leu Phe Asp Thr Ala
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Glu Val Tyr Ala Ala Gly Lys Ala Glu Val Ile Leu Gly Ser Ile Ile
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Lys Lys Lys Gly Trp Arg Arg Ser Ser Leu Val Ile Thr Thr Lys Leu
145 150 155 160
Tyr Trp Gly Gly Lys Ala Glu Thr Glu Arg Gly Leu Ser Arg Lys His
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Ile Ile Glu Gly Leu Lys Gly Ser Leu Gln Arg Leu Gln Leu Glu Tyr
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Val Asp Val Val Phe Ala Asn Arg Pro Asp Ser Asn Thr Pro Met Glu
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Glu Ile Val Arg Ala Met Thr His Val Ile Asn Gln Gly Met Ala Met
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Tyr Trp Gly Thr Ser Arg Trp Ser Ala Met Glu Ile Met Glu Ala Tyr
225 230 235 240
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245 250 255
Glu Tyr His Leu Phe Gln Arg Glu Lys Val Glu Val Gln Leu Pro Glu
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275 280 285
Cys Gly Ile Ile Ser Gly Lys Tyr Gly Asn Gly Val Pro Glu Ser Ser
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Arg Ala Ser Leu Lys Cys Tyr Gln Trp Leu Lys Glu Arg Ile Val Ser
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Glu Gln Leu Ile Glu Asn Leu Gly Ala Ile Gln Val Leu Pro Lys Met
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<210> 106
<211> 3103
<212> DNA
<213> Homo sapiens

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<210> 107
<211> 419
<212> PRT
<213> Homo sapiens

<400> 107
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Lys Ser Pro Lys Lys Ala Ser Glu Asn Ala Lys Asp Ser Ser Leu Ser
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Pro Ser Gly Glu Ser Gln Leu Arg Ala Arg Gln Leu Ala Leu Leu Arg
    50                  55                  60
Glu Val Glu Met Asn Trp Tyr Leu Lys Leu Cys Asp Leu Ser Ser Glu
65                  70                  75                  80
His Thr Thr Val Cys Thr Thr Gly Met Pro His Arg Asn Leu Gly Lys
                85                  90                  95
Ser Gly Leu Arg Val Ser Cys Leu Gly Leu Gly Thr Trp Val Thr Phe
            100                 105                 110
Gly Gly Gln Ile Ser Asp Glu Val Ala Glu Arg Leu Met Thr Ile Ala
        115                 120                 125
Tyr Glu Ser Gly Val Asn Leu Phe Asp Thr Ala Glu Val Tyr Ala Ala
    130                 135                 140
Gly Lys Ala Glu Val Ile Leu Gly Ser Ile Ile Lys Lys Lys Gly Trp
145                 150                 155                 160
Arg Arg Ser Ser Leu Val Ile Thr Thr Lys Leu Tyr Trp Gly Gly Lys
                165                 170                 175
Ala Glu Thr Glu Arg Gly Leu Ser Arg Lys His Ile Ile Glu Gly Leu
            180                 185                 190
Lys Gly Ser Leu Gln Arg Leu Gln Leu Glu Tyr Val Asp Val Val Phe
        195                 200                 205
Ala Asn Arg Pro Asp Ser Asn Thr Pro Met Glu Glu Ile Val Arg Ala
    210                 215                 220
Met Thr His Val Ile Asn Gln Gly Met Ala Met Tyr Trp Gly Thr Ser
225                 230                 235                 240
Arg Trp Ser Ala Met Glu Ile Met Glu Ala Tyr Ser Val Ala Arg Gln
                245                 250                 255
Phe Asn Met Ile Pro Pro Val Cys Glu Gln Ala Glu Tyr His Leu Phe
            260                 265                 270
Gln Arg Glu Lys Val Glu Val Gln Leu Pro Glu Leu Tyr His Lys Ile
        275                 280                 285
Gly Val Gly Ala Met Thr Trp Ser Pro Leu Ala Cys Gly Ile Ile Ser
    290                 295                 300
Gly Lys Tyr Gly Asn Gly Val Pro Glu Ser Ser Arg Ala Ser Leu Lys
305                 310                 315                 320
Cys Tyr Gln Trp Leu Lys Glu Arg Ile Val Ser Glu Glu Gly Arg Lys
                325                 330                 335
Gln Gln Asn Lys Leu Lys Asp Leu Ser Pro Ile Ala Glu Arg Leu Gly
            340                 345                 350
Cys Thr Leu Pro Gln Leu Ala Val Ala Trp Cys Leu Arg Asn Glu Gly
        355                 360                 365
Val Ser Ser Val Leu Leu Gly Ser Ser Thr Pro Glu Gln Leu Ile Glu
    370                 375                 380
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<211> 2620
<212> DNA
<213> Homo sapiens

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<211> 401
<212> PRT
<213> Homo sapiens

<400> 109
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Val Asn Ala Ala Arg Ala Lys Phe Arg Thr Val Ala Ile Ile Ala Arg
35 40 45

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Ser Leu Gly Thr Phe Thr Pro Gln His His Ile Ser Leu Lys Glu Ser
    50                  55                  60
Thr Ala Lys Gln Thr Gly Met Lys Tyr Arg Asn Leu Gly Lys Ser Gly
65                  70                  75                  80
Leu Arg Val Ser Cys Leu Gly Leu Gly Thr Trp Val Thr Phe Gly Gly
                85                  90                  95
Gln Ile Ser Asp Glu Val Ala Glu Arg Leu Met Thr Ile Ala Tyr Glu
            100                 105                 110
Ser Gly Val Asn Leu Phe Asp Thr Ala Glu Val Tyr Ala Ala Gly Lys
        115                 120                 125
Ala Glu Val Ile Leu Gly Ser Ile Ile Lys Lys Lys Gly Trp Arg Arg
    130                 135                 140
Ser Ser Leu Val Ile Thr Thr Lys Leu Tyr Trp Gly Gly Lys Ala Glu
145                 150                 155                 160
Thr Glu Arg Gly Leu Ser Arg Lys His Ile Ile Glu Gly Leu Lys Gly
                165                 170                 175
Ser Leu Gln Arg Leu Gln Leu Glu Tyr Val Asp Val Val Phe Ala Asn
            180                 185                 190
Arg Pro Asp Ser Asn Thr Pro Met Glu Glu Ile Val Arg Ala Met Thr
        195                 200                 205
His Val Ile Asn Gln Gly Met Ala Met Tyr Trp Gly Thr Ser Arg Trp
    210                 215                 220
Ser Ala Met Glu Ile Met Glu Ala Tyr Ser Val Ala Arg Gln Phe Asn
225                 230                 235                 240
Met Ile Pro Pro Val Cys Glu Gln Ala Glu Tyr His Leu Phe Gln Arg
                245                 250                 255
Glu Lys Val Glu Val Gln Leu Pro Glu Leu Tyr His Lys Ile Gly Val
            260                 265                 270
Gly Ala Met Thr Trp Ser Pro Leu Ala Cys Gly Ile Ile Ser Gly Lys
        275                 280                 285
Tyr Gly Asn Gly Val Pro Glu Ser Ser Arg Ala Ser Leu Lys Cys Tyr
    290                 295                 300
Gln Trp Leu Lys Glu Arg Ile Val Ser Glu Glu Gly Arg Lys Gln Gln
305                 310                 315                 320
Asn Lys Leu Lys Asp Leu Ser Pro Ile Ala Glu Arg Leu Gly Cys Thr
                325                 330                 335
Leu Pro Gln Leu Ala Val Ala Trp Cys Leu Arg Asn Glu Gly Val Ser
            340                 345                 350
Ser Val Leu Leu Gly Ser Ser Thr Pro Glu Gln Leu Ile Glu Asn Leu
        355                 360                 365
Gly Ala Ile Gln Val Leu Pro Lys Met Thr Ser His Val Val Asn Glu
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<210> 110
<211> 3944
<212> DNA
<213> Homo sapiens

<400> 110

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Ser Pro Ile Glu Ala Thr Pro Pro Gln Ser Leu Leu Glu Lys Val Ser
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Val Glu Arg Leu Glu Ile Arg Glu Gln Thr Lys Ser Lys Ser Glu Ala
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Val Pro Cys Asn Cys Asn Gly His Ser Asn Gln Cys Gln Asp Gly Ser
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Gly Ile Cys Val Asn Cys Gln His Asn Thr Ala Gly Glu His Cys Glu
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Arg Cys Gln Glu Gly Tyr Tyr Gly Asn Ala Val His Gly Ser Cys Arg
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Asn Gly Gly Asp Val Arg Cys Ser Cys Lys Ala Gly Tyr Thr Gly Thr
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Gln Cys Glu Arg Cys Ala Pro Gly Tyr Phe Gly Asn Pro Gln Lys Phe
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Ser Cys His Pro Leu Thr Gly Asp Cys Ile Asn Gln Glu Pro Lys Asp
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Ser Ser Pro Ala Glu Glu Cys Asp Asp Cys Asp Ser Cys Val Met Thr
        195   200   205
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Ser Gln Leu Gln Gly Leu Ser Ala Ser Ala Gly Leu Leu Glu Gln Met
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Arg His Met Glu Thr Gln Ala Lys Asp Leu Arg Asn Gln Leu Leu Asn
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Tyr Arg Ser Ala Ile Ser Asn His Gly Ser Lys Ile Glu Gly Leu Glu
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Glu Gly Asn Asn Val Pro Ser Gly Asp Phe Ser Arg Glu Trp Ala Glu
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Ala Gln Arg Met Met Arg Glu Leu Arg Asn Arg Asn Phe Gly Lys His
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Leu Arg Glu Ala Glu Ala Asp Lys Arg Glu Ser Gln Leu Leu Leu Asn
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Arg Ile Arg Thr Trp Gln Lys Thr His Gln Gly Glu Asn Asn Gly Leu
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965 970 975
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Phe Asp Phe Ser Thr Tyr Tyr Leu Gly Gly Ile Pro Ile Ala Ile Arg
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Thr Lys Lys Cys Ser Glu Asp Trp Lys Leu Val Arg Ser Ala Ser Phe
1140 1145 1150
Ser Arg Gly Gly Gln Leu Ser Phe Thr Asp Leu Gly Leu Pro Pro Thr
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Asp His Leu Gln Ala Ser Phe Gly Phe Gln Thr Phe Gln Pro Ser Gly
1170 1175 1180
Ile Leu Leu Asp His Gln Thr Trp Thr Arg Asn Leu Gln Val Thr Leu
1185 1190 1195 1200
Glu Asp Gly Tyr Ile Glu Leu Ser Thr Ser Asp Ser Gly Gly Pro Ile
1205 1210 1215
Phe Lys Ser Pro Gln Thr Tyr Met Asp Gly Leu Leu His Tyr Val Ser

1220 1225 1230
Val Ile Ser Asp Asn Ser Gly Leu Arg Leu Leu Ile Asp Asp Gln Leu
1235 1240 1245
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1250 1255 1260
Leu Arg Leu Gly Gly Ser Asn Phe Glu Gly Cys Ile Ser Asn Val Phe
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Val Gln Arg Leu Ser Leu Ser Pro Glu Val Leu Asp Leu Thr Ser Asn
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Pro Phe Leu Met Leu Leu Lys Gly Ser Thr Arg Phe Asn Lys Thr Lys
1315 1320 1325
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Arg Ser Val Lys Val Trp Gln Asp Ala Cys Ser Pro Leu Pro Lys Thr
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1410 1415 1420
Val Phe Ala Leu Gly Thr Asp Gly Lys Lys Leu Arg Ile Lys Ser Lys
1425 1430 1435 1440
Glu Lys Cys Asn Asp Gly Lys Trp His Thr Val Val Phe Gly His Asp
1445 1450 1455
Gly Glu Lys Gly Arg Leu Val Val Asp Gly Leu Arg Ala Arg Glu Gly
1460 1465 1470
Ser Leu Pro Gly Asn Ser Thr Ile Ser Ile Arg Ala Pro Val Tyr Leu
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1490 1495 1500
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Lys Gly Ile Tyr Phe Ser Glu Glu Gly Gly His Val Val Leu Ala His
1540 1545 1550
Ser Val Leu Leu Gly Pro Glu Phe Lys Leu Val Phe Ser Ile Arg Pro
1555 1560 1565
Arg Ser Leu Thr Gly Ile Leu Ile His Ile Gly Ser Gln Pro Gly Lys
1570 1575 1580
His Leu Cys Val Tyr Leu Glu Ala Gly Lys Val Thr Ala Ser Met Asp
1585 1590 1595 1600
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Cys Asp Gly Gln Trp His Ser Val Ala Val Thr Ile Lys Gln His Ile
1620 1625 1630
Leu His Leu Glu Leu Asp Thr Asp Ser Ser Tyr Thr Ala Gly Gln Ile
1635 1640 1645
Pro Phe Pro Pro Ala Ser Thr Gln Glu Pro Leu His Leu Gly Gly Ala
1650 1655 1660
Pro Ala Asn Leu Thr Thr Leu Arg Ile Pro Val Trp Lys Ser Phe Phe
1665 1670 1675 1680
Gly Cys Leu Arg Asn Ile His Val Asn His Ile Pro Val Pro Val Thr
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Gln

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<211> 5175
<212> DNA
<213> Homo sapiens

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<211> 1193
<212> PRT
<213> Homo sapiens

<400> 115
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            20   25   30
Lys Ser Arg Gln Cys Ile Phe Asp Arg Glu Leu His Arg Gln Thr Gly
        35   40   45
Asn Gly Phe Arg Cys Leu Asn Cys Asn Asp Asn Thr Asp Gly Ile His
    50   55   60
Cys Glu Lys Cys Lys Asn Gly Phe Tyr Arg His Arg Glu Arg Asp Arg
65   70   75   80
Cys Leu Pro Cys Asn Cys Asn Ser Lys Gly Ser Leu Ser Ala Arg Cys
                85   90   95

Asp Asn Ser Gly Arg Cys Ser Cys Lys Pro Gly Val Thr Gly Ala Arg
100 105 110
Cys Asp Arg Cys Leu Pro Gly Phe His Met Leu Thr Asp Ala Gly Cys
115 120 125
Thr Gln Asp Gln Arg Leu Leu Asp Ser Lys Cys Asp Cys Asp Pro Ala
130 135 140
Gly Ile Ala Gly Pro Cys Asp Ala Gly Arg Cys Val Cys Lys Pro Ala
145 150 155 160
Val Thr Gly Glu Arg Cys Asp Arg Cys Arg Ser Gly Tyr Tyr Asn Leu
165 170 175
Asp Gly Gly Asn Pro Glu Gly Cys Thr Gln Cys Phe Cys Tyr Gly His
180 185 190
Ser Ala Ser Cys Arg Ser Ser Ala Glu Tyr Ser Val His Lys Ile Thr
195 200 205
Ser Thr Phe His Gln Asp Val Asp Gly Trp Lys Ala Val Gln Arg Asn
210 215 220
Gly Ser Pro Ala Lys Leu Gln Trp Ser Gln Arg His Gln Asp Val Phe
225 230 235 240
Ser Ser Ala Gln Arg Leu Asp Pro Val Tyr Phe Val Ala Pro Ala Lys
245 250 255
Phe Leu Gly Asn Gln Gln Val Ser Tyr Gly Gln Ser Leu Ser Phe Asp
260 265 270
Tyr Arg Val Asp Arg Gly Gly Arg His Pro Ser Ala His Asp Val Ile
275 280 285
Leu Glu Gly Ala Gly Leu Arg Ile Thr Ala Pro Leu Met Pro Leu Gly
290 295 300
Lys Thr Leu Pro Cys Gly Leu Thr Lys Thr Tyr Thr Phe Arg Leu Asn
305 310 315 320
Glu His Pro Ser Asn Asn Trp Ser Pro Gln Leu Ser Tyr Phe Glu Tyr
325 330 335
Arg Arg Leu Leu Arg Asn Leu Thr Ala Leu Arg Ile Arg Ala Thr Tyr
340 345 350
Gly Glu Tyr Ser Thr Gly Tyr Ile Asp Asn Val Thr Leu Ile Ser Ala
355 360 365
Arg Pro Val Ser Gly Ala Pro Ala Pro Trp Val Glu Gln Cys Ile Cys
370 375 380
Pro Val Gly Tyr Lys Gly Gln Phe Cys Gln Asp Cys Ala Ser Gly Tyr
385 390 395 400
Lys Arg Asp Ser Ala Arg Leu Gly Pro Phe Gly Thr Cys Ile Pro Cys
405 410 415
Asn Cys Gln Gly Gly Gly Ala Cys Asp Pro Asp Thr Gly Asp Cys Tyr
420 425 430
Ser Gly Asp Glu Asn Pro Asp Ile Glu Cys Ala Asp Cys Pro Ile Gly
435 440 445
Phe Tyr Asn Asp Pro His Asp Pro Arg Ser Cys Lys Pro Cys Pro Cys
450 455 460
His Asn Gly Phe Ser Cys Ser Val Met Pro Glu Thr Glu Glu Val Val
465 470 475 480
Cys Asn Asn Cys Pro Pro Gly Val Thr Gly Ala Arg Cys Glu Leu Cys
485 490 495
Ala Asp Gly Tyr Phe Gly Asp Pro Phe Gly Glu His Gly Pro Val Arg
500 505 510
Pro Cys Gln Pro Cys Gln Cys Asn Asn Asn Val Asp Pro Ser Ala Ser
515 520 525
Gly Asn Cys Asp Arg Leu Thr Gly Arg Cys Leu Lys Cys Ile His Asn
530 535 540
Thr Ala Gly Ile Tyr Cys Asp Gln Cys Lys Ala Gly Tyr Phe Gly Asp
545 550 555 560
Pro Leu Ala Pro Asn Pro Ala Asp Lys Cys Arg Ala Cys Asn Cys Asn

565 570 575
Pro Met Gly Ser Glu Pro Val Gly Cys Arg Ser Asp Gly Thr Cys Val
580 585 590
Cys Lys Pro Gly Phe Gly Gly Pro Asn Cys Glu His Gly Ala Phe Ser
595 600 605
Cys Pro Ala Cys Tyr Asn Gln Val Lys Ile Gln Met Asp Gln Phe Met
610 615 620
Gln Gln Leu Gln Arg Met Glu Ala Leu Ile Ser Lys Ala Gln Gly Gly
625 630 635 640
Asp Gly Val Val Pro Asp Thr Glu Leu Glu Gly Arg Met Gln Gln Ala
645 650 655
Glu Gln Ala Leu Gln Asp Ile Leu Arg Asp Ala Gln Ile Ser Glu Gly
660 665 670
Ala Ser Arg Ser Leu Gly Leu Gln Leu Ala Lys Val Arg Ser Gln Glu
675 680 685
Asn Ser Tyr Gln Ser Arg Leu Asp Asp Leu Lys Met Thr Val Glu Arg
690 695 700
Val Arg Ala Leu Gly Ser Gln Tyr Gln Asn Arg Val Arg Asp Thr His
705 710 715 720
Arg Leu Ile Thr Gln Met Gln Leu Ser Leu Ala Glu Ser Glu Ala Ser
725 730 735
Leu Gly Asn Thr Asn Ile Pro Ala Ser Asp His Tyr Val Gly Pro Asn
740 745 750
Gly Phe Lys Ser Leu Ala Gln Glu Ala Thr Arg Leu Ala Glu Ser His
755 760 765
Val Glu Ser Ala Ser Asn Met Glu Gln Leu Thr Arg Glu Thr Glu Asp
770 775 780
Tyr Ser Lys Gln Ala Leu Ser Leu Val Arg Lys Ala Leu His Glu Gly
785 790 795 800
Val Gly Ser Gly Ser Gly Ser Pro Asp Gly Ala Val Val Gln Gly Leu
805 810 815
Val Glu Lys Leu Glu Lys Thr Lys Ser Leu Ala Gln Gln Leu Thr Arg
820 825 830
Glu Ala Thr Gln Ala Glu Ile Glu Ala Asp Arg Ser Tyr Gln His Ser
835 840 845
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850 855 860
Ser Phe Gln Val Glu Glu Ala Lys Arg Ile Lys Gln Lys Ala Asp Ser
865 870 875 880
Leu Ser Thr Leu Val Thr Arg His Met Asp Glu Phe Lys Arg Thr Gln
885 890 895
Lys Asn Leu Gly Asn Trp Lys Glu Glu Ala Gln Gln Leu Leu Gln Asn
900 905 910
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915 920 925
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930 935 940
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980 985 990
Ala Glu Arg Ala Leu Gly Ser Ala Ala Ala Asp Ala Gln Arg Ala Lys
995 1000 1005
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Ile Gly Ser Leu Asn Leu Glu Ala Asn Val Thr Ala Asp Gly Ala Leu
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1060 1065 1070
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1075 1080 1085
Lys Asn Ala Gly Val Thr Ile Gln Asp Thr Leu Asn Thr Leu Asp Gly
1090 1095 1100
Leu Leu His Leu Met Asp Gln Pro Leu Ser Val Asp Glu Glu Gly Leu
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Val Leu Leu Glu Gln Lys Leu Ser Arg Ala Lys Thr Gln Ile Asn Ser
1125 1130 1135
Gln Leu Arg Pro Met Met Ser Glu Leu Glu Glu Arg Ala Arg Gln Gln
1140 1145 1150
Arg Gly His Leu His Leu Leu Glu Thr Ser Ile Asp Gly Ile Leu Ala
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1185 1190

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<211> 749
<212> DNA
<213> Homo sapiens

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35 40 45
Met Val Leu Glu Asp Val Thr Glu Phe Glu Ile Thr Pro Glu Gly Arg
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Met Leu Val Pro Gly Gly Glu Gly Pro Glu Val

85 90

<210> 118
<211> 1717
<212> DNA
<213> Homo sapiens

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atgcacttaa agaagtattt ttagaataag aatttgcata cttacctagt gaaactttc 1620
tagaattatt tttcactcta agtcatgtat gtttctcttt gattatttgc atgttatgtt 1680
taataagcta ctagcaaaat aaaacatagc aaatggc 1717

<210> 119
<211> 338
<212> PRT
<213> Homo sapiens

<400> 119
Met Ser Leu Ser Ala Phe Thr Leu Phe Leu Ala Leu Ile Gly Gly Thr
1 5 10 15
Ser Gly Gln Tyr Tyr Asp Tyr Asp Phe Pro Leu Ser Ile Tyr Gly Gln
20 25 30
Ser Ser Pro Asn Cys Ala Pro Glu Cys Asn Cys Pro Glu Ser Tyr Pro
35 40 45
Ser Ala Met Tyr Cys Asp Glu Leu Lys Leu Lys Ser Val Pro Met Val
50 55 60
Pro Pro Gly Ile Lys Tyr Leu Tyr Leu Arg Asn Asn Gln Ile Asp His
65 70 75 80
Ile Asp Glu Lys Ala Phe Glu Asn Val Thr Asp Leu Gln Trp Leu Ile
85 90 95
Leu Asp His Asn Leu Leu Glu Asn Ser Lys Ile Lys Gly Arg Val Phe
100 105 110

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Ser Lys Leu Lys Gln Leu Lys Lys Leu His Ile Asn His Asn Asn Leu
        115                 120                 125
Thr Glu Ser Val Gly Pro Leu Pro Lys Ser Leu Glu Asp Leu Gln Leu
    130                 135                 140
Thr His Asn Lys Ile Thr Lys Leu Gly Ser Phe Glu Gly Leu Val Asn
145                 150                 155                 160
Leu Thr Phe Ile His Leu Gln His Asn Arg Leu Lys Glu Asp Ala Val
                165                 170                 175
Ser Ala Ala Phe Lys Gly Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser
            180                 185                 190
Phe Asn Gln Ile Ala Arg Leu Pro Ser Gly Leu Pro Val Ser Leu Leu
        195                 200                 205
Thr Leu Tyr Leu Asp Asn Asn Lys Ile Ser Asn Ile Pro Asp Glu Tyr
    210                 215                 220
Phe Lys Arg Phe Asn Ala Leu Gln Tyr Leu Arg Leu Ser His Asn Glu
225                 230                 235                 240
Leu Ala Asp Ser Gly Ile Pro Gly Asn Ser Phe Asn Val Ser Ser Leu
                245                 250                 255
Val Glu Leu Asp Leu Ser Tyr Asn Lys Leu Lys Asn Ile Pro Thr Val
            260                 265                 270
Asn Glu Asn Leu Glu Asn Tyr Tyr Leu Glu Val Asn Gln Leu Glu Lys
        275                 280                 285
Phe Asp Ile Lys Ser Phe Cys Lys Ile Leu Gly Pro Leu Ser Tyr Ser
    290                 295                 300
Lys Ile Lys His Leu Arg Leu Asp Gly Asn Arg Ile Ser Glu Thr Ser
305                 310                 315                 320
Leu Pro Pro Asp Met Tyr Glu Cys Leu Arg Val Ala Asn Glu Val Thr
                325                 330                 335
Leu Asn
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<210> 120
<211> 1334
<212> DNA
<213> Homo sapiens

<400> 120
gcagaccccc atcatgggca gccagagctc caaggctccc cggggcgacg tgaccgccga 60
ggaggcagca ggcgcttccc ccgcgaaggc caacggccag gagaatggcc acgtgaaaag 120
caatggagac ttatccccca agggtgaagg ggagtcgccc cctgtgaacg gaacagatga 180
ggcagccggg gccactggcg atgccatcga gccagcaccc cctagccagg gtgctgaggc 240
caagggggag gtcccccca aggagacccc caagaagaag aagaaattct ctttcaagaa 300
gcctttcaaa ttgagcggcc tgtccttcaa gagaaatcgg aaggagggtg gggtgattc 360
ttctgcctcc tcacccacag aggaagagca ggagcagggg gagatcggtg cctgcagcga 420
cgagggcact gctcaggaag ggaaggccgc agccacccct gagagccagg aaccccaggc 480
caagggggca gaggctagtg cagcctcaga agaagaggca gggccccagg ctacagagcc 540
atccactccc tcggggccgg agagtggccc tacaccagcc agcgctgagc agaatgagta 600
gctaggtagg ggcaggtggg tgatctctaa gctgcaaaaa ctgtgctgtc cttgtgaggt 660
cactgcctgg acctggtgcc ctggctgcct tcctgtgccc agaaaggaag ggctattgc 720
ctcctcccag ccacgttccc tttcctcctc tccctcctgt ggattctccc atcagccatc 780
tggttctcct cttaaggcca gttgaagatg gtcccttaca gcttcccaag ttaggttagt 840
gatgtgaaat gctcctgtcc ctggccctac ctccttccct gtccccaccc ctgcataagg 900
cagttgttgg ttttcttccc caattctttt ccaagtaggt tttgtttacc ctactcccca 960
aatccctgag ccagaagtgg ggtgcttata ctcccaaacc ttgagtgtcc agccttcccc 1020
tgttgttttt agtctcttgt gctgtgccta gtggcacctg ggctggggag gacactgccc 1080
cgtctaggtt tttataaatg tcttactcaa gttcaaacct ccagcctgtg aatcaactgt 1140
gtctcttttt tgacttggta agcaagtatt aggctttggg gtggggggag gtctgtaatg 1200
tgaaacaact tcttgtcttt ttttctccca ctgttgtaaa taacttttaa tggccaaacc 1260
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ccagatttgt actttttttt tttttctaac tgctaaaacc attctcttcc acctggtttt 1320
actgtaacat ttgg 1334

<210> 121
<211> 195
<212> PRT
<213> Homo sapiens

<400> 121
Met Gly Ser Gln Ser Ser Lys Ala Pro Arg Gly Asp Val Thr Ala Glu
1 5 10 15
Glu Ala Ala Gly Ala Ser Pro Ala Lys Ala Asn Gly Gln Glu Asn Gly
20 25 30
His Val Lys Ser Asn Gly Asp Leu Ser Pro Lys Gly Glu Gly Glu Ser
35 40 45
Pro Pro Val Asn Gly Thr Asp Glu Ala Ala Gly Ala Thr Gly Asp Ala
50 55 60
Ile Glu Pro Ala Pro Pro Ser Gln Gly Ala Glu Ala Lys Gly Glu Val
65 70 75 80
Pro Pro Lys Glu Thr Pro Lys Lys Lys Lys Lys Phe Ser Phe Lys Lys
85 90 95
Pro Phe Lys Leu Ser Gly Leu Ser Phe Lys Arg Asn Arg Lys Glu Gly
100 105 110
Gly Gly Asp Ser Ser Ala Ser Ser Pro Thr Glu Glu Glu Gln Glu Gln
115 120 125
Gly Glu Ile Gly Ala Cys Ser Asp Glu Gly Thr Ala Gln Glu Gly Lys
130 135 140
Ala Ala Ala Thr Pro Glu Ser Gln Glu Pro Gln Ala Lys Gly Ala Glu
145 150 155 160
Ala Ser Ala Ala Ser Glu Glu Glu Ala Gly Pro Gln Ala Thr Glu Pro
165 170 175
Ser Thr Pro Ser Gly Pro Glu Ser Gly Pro Thr Pro Ala Ser Ala Glu
180 185 190
Gln Asn Glu
195

<210> 122
<211> 1081
<212> DNA
<213> Homo sapiens

<400> 122
attgcaactt ggtctcacag tggcttaggc cagggtggga gcagtgaacg gagtcacaaa 60
agaaattttt cagctgtcct ctctgacacc accccggcct gcctctttgt tgccatgaga 120
gctgcctacc tcttcctgct attcctgcct gcaggcttgc tggctcaggg ccagtatgat 180
ctggacccgc tgccgccgtt ccctgaccac gtccagtaca cccactatag cgaccagatc 240
gacaacccag actactatga ttatcaagag gtgactcctc ggccctccga ggaacagttc 300
cagttccagt cccagcagca agtccaacag gaagtcatcc cagccccaac cccagaacca 360
ggaaatgcag agctggagcc cacagagcct gggcctcttg actgccgtga ggaacagtac 420
ccgtgcaccc gcctctactc catacacagg ccttgcaaac agtgtctcaa cgaggtctgc 480
ttctacagcc tccgccgtgt gtacgtcatt aacaaggaga tctgtgttcg tacagtgtgt 540
gcccacgagg agctcctccg agctgacctc tgtcgggaca agttctccaa atgtggcgtg 600
atggccagca gcggcctgtg ccaatccgtg gcggcctcct gtgccaggag ctgtgggagc 660
tgctagggtg gtgctggcat cctgagtcct ggccctcctg ggatctgggg ccctcgggct 720
acctgacctg gtgctttttt ccccatcccc atgttccttt tattctgaaa aagttagtgg 780
actgcagccc tgggggttgc aggctgcggt gcctcaggcc cctccttcag cctgtggcca 840
cctctggggc acgatggggg ctccccactg cccagtctgc ccctcgggtt gggggagtat 900
cccaggcctc tctgtgggac ctgggcctga cgggcccttc tcagcccgtt ttgaggacag 960

acagtccccc gaggtaggct acatcccccc accccagctg gtctgcttgg atttcctaca 1020
gcccccgtgg gcatggacca cctttatttt atacaaaatt aaaaacaagt ttttacaaaa 1080
a 1081

<210> 123
<211> 183
<212> PRT
<213> Homo sapiens

<400> 123
Met Arg Ala Ala Tyr Leu Phe Leu Leu Phe Leu Pro Ala Gly Leu Leu
1 5 10 15
Ala Gln Gly Gln Tyr Asp Leu Asp Pro Leu Pro Pro Phe Pro Asp His
20 25 30
Val Gln Tyr Thr His Tyr Ser Asp Gln Ile Asp Asn Pro Asp Tyr Tyr
35 40 45
Asp Tyr Gln Glu Val Thr Pro Arg Pro Ser Glu Glu Gln Phe Gln Phe
50 55 60
Gln Ser Gln Gln Gln Val Gln Gln Glu Val Ile Pro Ala Pro Thr Pro
65 70 75 80
Glu Pro Gly Asn Ala Glu Leu Glu Pro Thr Glu Pro Gly Pro Leu Asp
85 90 95
Cys Arg Glu Glu Gln Tyr Pro Cys Thr Arg Leu Tyr Ser Ile His Arg
100 105 110
Pro Cys Lys Gln Cys Leu Asn Glu Val Cys Phe Tyr Ser Leu Arg Arg
115 120 125
Val Tyr Val Ile Asn Lys Glu Ile Cys Val Arg Thr Val Cys Ala His
130 135 140
Glu Glu Leu Leu Arg Ala Asp Leu Cys Arg Asp Lys Phe Ser Lys Cys
145 150 155 160
Gly Val Met Ala Ser Ser Gly Leu Cys Gln Ser Val Ala Ala Ser Cys
165 170 175
Ala Arg Ser Cys Gly Ser Cys
180

<210> 124
<211> 1066
<212> DNA
<213> Homo sapiens

<400> 124
ggccaagggg cggctccggc gggcggactc ggagcgggcg gcggagtgac ccggacagct 60
gtcctctctg acaccacccc ggcctgcctc tttgttgcca tgagagctgc ctacctcttc 120
ctgctattcc tgcctgcagg cttgctggct cagggccagt atgatctgga cccgctgccg 180
ccgttccctg accacgtcca gtacacccac tatagcgacc agatcgacaa cccagactac 240
tatgattatc aagaggtgac tcctcggccc tccgaggaac agttccagtt ccagtcccag 300
cagcaagtcc aacaggaagt catcccagcc ccaaccccag aaccaggaaa tgcagagctg 360
gagcccacag agcctgggcc tcttgactgc cgtgaggaac agtacccgtg cacccgcctc 420
tactccatac acaggccttg caaacagtgt ctcaacgagg tctgcttcta cagcctccgc 480
cgtgtgtacg tcattaacaa ggagatctgt gttcgtacag tgtgtgccca cgaggagctc 540
ctccgagctg acctctgtcg ggacaagttc tccaaatgtg gcgtgatggc cagcagcggc 600
ctgtgccaat ccgtggcggc ctcctgtgcc aggagctgtg ggagctgcta gggtggtgct 660
ggcatcctga gtcctggccc tcctgggatc tggggccctc gggctacctg acctggtgct 720
tttttcccca tccccatgtt ccttttattc tgaaaaagtt agtggactgc agccctgggg 780
gttgcaggct gcggtgcctc aggcccctcc ttcagcctgt ggccacctct ggggcacgat 840
gggggctccc cactgcccag tctgcccctc gggttggggg agtatcccag gcctctctgt 900
gggacctggg cctgacgggc ccttctcagc ccgttttgag gacagacagt cccccgaggt 960
aggctacatc cccccacccc agctggtctg cttggatttc ctacagcccc cgtgggcatg 1020

gaccaccttt attttataca aaattaaaaa caagttttta caaaaa 1066

<210> 125
<211> 183
<212> PRT
<213> Homo sapiens

<400> 125
Met Arg Ala Ala Tyr Leu Phe Leu Leu Phe Leu Pro Ala Gly Leu Leu
1 5 10 15
Ala Gln Gly Gln Tyr Asp Leu Asp Pro Leu Pro Pro Phe Pro Asp His
20 25 30
Val Gln Tyr Thr His Tyr Ser Asp Gln Ile Asp Asn Pro Asp Tyr Tyr
35 40 45
Asp Tyr Gln Glu Val Thr Pro Arg Pro Ser Glu Glu Gln Phe Gln Phe
50 55 60
Gln Ser Gln Gln Gln Val Gln Gln Glu Val Ile Pro Ala Pro Thr Pro
65 70 75 80
Glu Pro Gly Asn Ala Glu Leu Glu Pro Thr Glu Pro Gly Pro Leu Asp
85 90 95
Cys Arg Glu Glu Gln Tyr Pro Cys Thr Arg Leu Tyr Ser Ile His Arg
100 105 110
Pro Cys Lys Gln Cys Leu Asn Glu Val Cys Phe Tyr Ser Leu Arg Arg
115 120 125
Val Tyr Val Ile Asn Lys Glu Ile Cys Val Arg Thr Val Cys Ala His
130 135 140
Glu Glu Leu Leu Arg Ala Asp Leu Cys Arg Asp Lys Phe Ser Lys Cys
145 150 155 160
Gly Val Met Ala Ser Ser Gly Leu Cys Gln Ser Val Ala Ala Ser Cys
165 170 175
Ala Arg Ser Cys Gly Ser Cys
180

<210> 126
<211> 1611
<212> DNA
<213> Homo sapiens

<400> 126
acataatttc tggagccctg taccaacgtg tggccacata ttctgtcagg aaccctgtgt 60
gatcatggtc tggatctgca acacgggcca ggccaaagtc acagatcttg agatcacagg 120
tggtgttgag cagcaggcag gcaggcaatc ggtccgagtg gctgtcggct cttcagctct 180
ccgctcggcg tcttccttcc tctcccggtc agcgtcggcg gctgcaccgg cggcgggcag 240
tcctgcggga ggggcgacaa gagctgaggc gcggccgccg agcgtcgagc tcagcgcggc 300
ggaggcggcg gcggcccggc agccaacatg gcggcggcgg cggcggcggg cgcgggcccg 360
gagatggtcc gcgggcaggt gttcgacgtg gggccgcgct acaccaacct ctcgtacatc 420
ggcgagggcg cctacggcat ggtgtgctct gcttatgata atgtcaacaa agttcgagta 480
gctatcaaga aaatcagccc ctttgagcac cagacctact gccagagaac cctgagggag 540
ataaaaatct tactgcgctt cagacatgag aacatcattg gaatcaatga cattattcga 600
gcaccaacca tcgagcaaat gaaagatgta tatatagtac aggacctcat ggaaacagat 660
ctttacaagc tcttgaagac acaacacctc agcaatgacc atatctgcta ttttctctac 720
cagatcctca gagggttaaa atatatccat tcagctaacg ttctgcaccg tgacctcaag 780
ccttccaacc tgctgctcaa caccacctgt gatctcaaga tctgtgactt tggcctggcc 840
cgtgttgcag atccagacca tgatcacaca gggttcctga cagaatatgt ggccacacgt 900
tggtacaggg ctccagaaat tatgttgaat tccaagggct acaccaagtc cattgatatt 960
tggtctgtag gctgcattct ggcagaaatg ctttccaaca ggcccatctt tccagggaag 1020
cattatcttg accagctgaa tcacattttg ggtattcttg gatccccatc acaagaagac 1080
ctgaattgta taataaattt aaaagctagg aactatttgc tttctcttcc acacaaaaat 1140

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aaggtgccat ggaacaggct gttcccaaat gctgactcca aagctctgga cttattggac 1200
aaaatgttga cattcaaccc acacaagagg attgaagtag aacaggctct ggcccaccca 1260
tatctggagc agtattacga cccgagtgac gagcccatcg ccgaagcacc attcaagttc 1320
gacatggaat tggatgactt gcctaaggaa aagctaaaag aactaatttt tgaagagact 1380
gctagattcc agccaggata cagatcttaa atttgtcagg acaagggctc agaggactgg 1440
acgtgctcag acatcggtgt tcttcttccc agttcttgac ccctggtcct gtctccagcc 1500
cgtcttggct tatccacttt gactcctttg agccgtttgg aggggcggtt tctggtagtt 1560
gtggctttta tgctttcaaa gaatttcttc agtccagaga attcactggc c          1611
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<210> 127
<211> 360
<212> PRT
<213> Homo sapiens

<400> 127

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Met Ala Ala Ala Ala Ala Ala Gly Ala Gly Pro Glu Met Val Arg Gly
 1               5                  10                  15
Gln Val Phe Asp Val Gly Pro Arg Tyr Thr Asn Leu Ser Tyr Ile Gly
            20                  25                  30
Glu Gly Ala Tyr Gly Met Val Cys Ser Ala Tyr Asp Asn Val Asn Lys
        35                  40                  45
Val Arg Val Ala Ile Lys Lys Ile Ser Pro Phe Glu His Gln Thr Tyr
    50                  55                  60
Cys Gln Arg Thr Leu Arg Glu Ile Lys Ile Leu Leu Arg Phe Arg His
65                  70                  75                  80
Glu Asn Ile Ile Gly Ile Asn Asp Ile Ile Arg Ala Pro Thr Ile Glu
                85                  90                  95
Gln Met Lys Asp Val Tyr Ile Val Gln Asp Leu Met Glu Thr Asp Leu
            100                 105                 110
Tyr Lys Leu Leu Lys Thr Gln His Leu Ser Asn Asp His Ile Cys Tyr
        115                 120                 125
Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala Asn
    130                 135                 140
Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu Leu Leu Asn Thr Thr
145                 150                 155                 160
Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala Arg Val Ala Asp Pro
                165                 170                 175
Asp His Asp His Thr Gly Phe Leu Thr Glu Tyr Val Ala Thr Arg Trp
            180                 185                 190
Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys Gly Tyr Thr Lys Ser
        195                 200                 205
Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala Glu Met Leu Ser Asn
    210                 215                 220
Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp Gln Leu Asn His Ile
225                 230                 235                 240
Leu Gly Ile Leu Gly Ser Pro Ser Gln Glu Asp Leu Asn Cys Ile Ile
                245                 250                 255
Asn Leu Lys Ala Arg Asn Tyr Leu Leu Ser Leu Pro His Lys Asn Lys
            260                 265                 270
Val Pro Trp Asn Arg Leu Phe Pro Asn Ala Asp Ser Lys Ala Leu Asp
        275                 280                 285
Leu Leu Asp Lys Met Leu Thr Phe Asn Pro His Lys Arg Ile Glu Val
    290                 295                 300
Glu Gln Ala Leu Ala His Pro Tyr Leu Glu Gln Tyr Tyr Asp Pro Ser
305                 310                 315                 320
Asp Glu Pro Ile Ala Glu Ala Pro Phe Lys Phe Asp Met Glu Leu Asp
                325                 330                 335
Asp Leu Pro Lys Glu Lys Leu Lys Glu Leu Ile Phe Glu Glu Thr Ala
            340                 345                 350
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Arg Phe Gln Pro Gly Tyr Arg Ser
        355   360

<210> 128
<211> 2917
<212> DNA
<213> Homo sapiens

<400> 128
ggaaaaaagc gacttgtggc ggtcgagcgt ggcgcaggcg aatcctcggc actaagcaaa 60
tatggacctc gcggcggcag cggagccggg cgccggcagc cagcacctgg aggtccgcga 120
cgaggtggcc gagaagtgcc agaaactgtt cctggacttc ttggaggagt ttcagagcag 180
cgatggagaa attaaatact tgcaattagc agaggaactg attcgtcctg agagaaacac 240
attggttgtg agttttgtgg acctggaaca atttaaccag caactttcca ccaccattca 300
agaggagttc tatagagttt acccttacct gtgtcgggcc ttgaaaacat tcgtcaaaga 360
ccgtaaagag atccctcttg ccaaggattt ttatgttgca ttccaagacc tgcctaccag 420
acacaagatt cgagagctca cctcatccag aattggtttg ctcactcgca tcagtgggca 480
ggtggtgcgg actcacccag ttcacccaga gcttgtgagc ggaacttttc tgtgcttgga 540
ctgtcagaca gtgatcaggg atgtagaaca gcagttcaaa tacacacagc caaacatctg 600
ccgaaatcca gtttgtgcca acaggaggag attcttactg gatacaaata aatcaagatt 660
tgttgatttt caaaaggttc gtattcaaga gacccaagct gagcttcctc gagggagtat 720
cccccgcagt ttagaagtaa ttttaagggc tgaagctgtg gaatcagctc aagctggtga 780
caagtgtgac tttacaggga cactgattgt tgtgcctgac gtctccaagc ttagcacacc 840
aggagcacgt gcagaaacta attcccgtgt cagtggtgtt gatggatatg agacagaagg 900
cattcgagga ctccgggccc ttggtgttag ggacctttct tataggctgg tctttcttgc 960
ctgctgtgtt gcgccaacca acccaaggtt tggggggaaa gagctcagag atgaggaaca 1020
gacagctgag agcattaaga accaaatgac tgtgaaagaa tgggagaaag tgtttgagat 1080
gagtcaagat aaaaatctat accacaatct ttgtaccagc ctgttcccta ctatacatgg 1140
caatgatgaa gtaaaacggg gtgtcctgct gatgctcttt ggtggcgttc caaagacaac 1200
aggagaaggg acctctcttc gaggggacat aaatgtttgc attgttggtg acccaagtac 1260
agctaagagc caatttctca agcacgtgga ggagttcagc cccagagctg tctacaccag 1320
tggtaaagcg tccagtgctg ctggcttaac agcagctgtt gtgagagatg aagaatctca 1380
tgagtttgtc attgaggctg gagctttgat gttggctgat aatggtgtgt gttgtattga 1440
tgaatttgat aagatggacg tgcgggatca agttgctatt catgaagcta tggaacagca 1500
gaccatatcc atcactaaag caggagtgaa ggctactctg aacgcccgga cgtccatttt 1560
ggcagcagca aacccaatca gtggacacta tgacagatca aaatcattga aacagaatat 1620
aaatttgtca gctcccatca tgtcccgatt cgatctcttc tttatccttg tggatgaatg 1680
taatgaggtt acagattatg ccattgccag gcgcatagta gatttgcatt caagaattga 1740
ggaatcaatt gatcgtgtct attccctcga tgatatcaga agatatcttc tctttgcaag 1800
acagtttaaa cccaagattt ccaaagagtc agaggacttc attgtggagc aatataaaca 1860
tctccgccag agagatggtt ctggagtgac caagtcttca tggaggatta cagtgcgaca 1920
gcttgagagc atgattcgtc tctctgaagc tatggctcgg atgcactgct gtgatgaggt 1980
ccaacctaaa catgtgaagg aagctttccg gttactgaat aaatcaatca tccgtgtgga 2040
aacacctgat gtcaatctag atcaagagga agagatccag atggaggtag atgagggtgc 2100
tggtggcatc aatggtcatg ctgacagccc tgctcctgtg aacgggatca atggctacaa 2160
tgaagacata aatcaagagt ctgctcccaa agcctcctta aggctgggct tctctgagta 2220
ctgccgaatc tctaacctta ttgtgcttca cctcagaaag gtggaagaag aagaggacga 2280
gtcagcatta aagaggagcg agcttgttaa ctggtacttg aaggaaatcg aatcagagat 2340
agactctgaa gaagaactta taaataaaaa aagaatcata gagaaagtta ttcatcgact 2400
cacacactat gatcatgttc taattgagct cacccaggct ggattgaaag gctccacaga 2460
gggaagtgag agctatgaag aagatcccta cttggtagtt aaccctaact acttgctcga 2520
agattgagat agtgaaagta actgaccaga gctgaggaac tgtggcacag cacctcgtgg 2580
cctggagcct ggctggagct ctgctaggga cagaagtgtt tctggaagtg atgcttccag 2640
gatttgtttt cagaaacaag aattgagttg atggtcctat gtgtcacatt catcacaggt 2700
ttcataccaa cacaggcttc agcacttcct ttggtgtgtt tcctgtccca gtgaagttgg 2760
aaccaaataa tgtgtagtct ctataaccaa tacctttgtt ttcatgtgta agaaaaggcc 2820
cattactttt aaggtatgtg ctgtcctatt gagcaaataa ctttttttca attgccagct 2880
actgctttta ttcatcaaaa taaaataact tgttctg 2917

<210> 129
<211> 821
<212> PRT
<213> Homo sapiens

<400> 129
Met Asp Leu Ala Ala Ala Ala Glu Pro Gly Ala Gly Ser Gln His Leu
1 5 10 15
Glu Val Arg Asp Glu Val Ala Glu Lys Cys Gln Lys Leu Phe Leu Asp
20 25 30
Phe Leu Glu Glu Phe Gln Ser Ser Asp Gly Glu Ile Lys Tyr Leu Gln
35 40 45
Leu Ala Glu Glu Leu Ile Arg Pro Glu Arg Asn Thr Leu Val Val Ser
50 55 60
Phe Val Asp Leu Glu Gln Phe Asn Gln Gln Leu Ser Thr Thr Ile Gln
65 70 75 80
Glu Glu Phe Tyr Arg Val Tyr Pro Tyr Leu Cys Arg Ala Leu Lys Thr
85 90 95
Phe Val Lys Asp Arg Lys Glu Ile Pro Leu Ala Lys Asp Phe Tyr Val
100 105 110
Ala Phe Gln Asp Leu Pro Thr Arg His Lys Ile Arg Glu Leu Thr Ser
115 120 125
Ser Arg Ile Gly Leu Leu Thr Arg Ile Ser Gly Gln Val Val Arg Thr
130 135 140
His Pro Val His Pro Glu Leu Val Ser Gly Thr Phe Leu Cys Leu Asp
145 150 155 160
Cys Gln Thr Val Ile Arg Asp Val Glu Gln Gln Phe Lys Tyr Thr Gln
165 170 175
Pro Asn Ile Cys Arg Asn Pro Val Cys Ala Asn Arg Arg Arg Phe Leu
180 185 190
Leu Asp Thr Asn Lys Ser Arg Phe Val Asp Phe Gln Lys Val Arg Ile
195 200 205
Gln Glu Thr Gln Ala Glu Leu Pro Arg Gly Ser Ile Pro Arg Ser Leu
210 215 220
Glu Val Ile Leu Arg Ala Glu Ala Val Glu Ser Ala Gln Ala Gly Asp
225 230 235 240
Lys Cys Asp Phe Thr Gly Thr Leu Ile Val Val Pro Asp Val Ser Lys
245 250 255
Leu Ser Thr Pro Gly Ala Arg Ala Glu Thr Asn Ser Arg Val Ser Gly
260 265 270
Val Asp Gly Tyr Glu Thr Glu Gly Ile Arg Gly Leu Arg Ala Leu Gly
275 280 285
Val Arg Asp Leu Ser Tyr Arg Leu Val Phe Leu Ala Cys Cys Val Ala
290 295 300
Pro Thr Asn Pro Arg Phe Gly Gly Lys Glu Leu Arg Asp Glu Glu Gln
305 310 315 320
Thr Ala Glu Ser Ile Lys Asn Gln Met Thr Val Lys Glu Trp Glu Lys
325 330 335
Val Phe Glu Met Ser Gln Asp Lys Asn Leu Tyr His Asn Leu Cys Thr
340 345 350
Ser Leu Phe Pro Thr Ile His Gly Asn Asp Glu Val Lys Arg Gly Val
355 360 365
Leu Leu Met Leu Phe Gly Gly Val Pro Lys Thr Thr Gly Glu Gly Thr
370 375 380
Ser Leu Arg Gly Asp Ile Asn Val Cys Ile Val Gly Asp Pro Ser Thr
385 390 395 400
Ala Lys Ser Gln Phe Leu Lys His Val Glu Glu Phe Ser Pro Arg Ala
405 410 415

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Val Tyr Thr Ser Gly Lys Ala Ser Ser Ala Ala Gly Leu Thr Ala Ala
                420                 425                 430
Val Val Arg Asp Glu Glu Ser His Glu Phe Val Ile Glu Ala Gly Ala
        435                 440                 445
Leu Met Leu Ala Asp Asn Gly Val Cys Cys Ile Asp Glu Phe Asp Lys
    450                 455                 460
Met Asp Val Arg Asp Gln Val Ala Ile His Glu Ala Met Glu Gln Gln
465                 470                 475                 480
Thr Ile Ser Ile Thr Lys Ala Gly Val Lys Ala Thr Leu Asn Ala Arg
                485                 490                 495
Thr Ser Ile Leu Ala Ala Ala Asn Pro Ile Ser Gly His Tyr Asp Arg
            500                 505                 510
Ser Lys Ser Leu Lys Gln Asn Ile Asn Leu Ser Ala Pro Ile Met Ser
        515                 520                 525
Arg Phe Asp Leu Phe Phe Ile Leu Val Asp Glu Cys Asn Glu Val Thr
    530                 535                 540
Asp Tyr Ala Ile Ala Arg Arg Ile Val Asp Leu His Ser Arg Ile Glu
545                 550                 555                 560
Glu Ser Ile Asp Arg Val Tyr Ser Leu Asp Asp Ile Arg Arg Tyr Leu
                565                 570                 575
Leu Phe Ala Arg Gln Phe Lys Pro Lys Ile Ser Lys Glu Ser Glu Asp
            580                 585                 590
Phe Ile Val Glu Gln Tyr Lys His Leu Arg Gln Arg Asp Gly Ser Gly
        595                 600                 605
Val Thr Lys Ser Ser Trp Arg Ile Thr Val Arg Gln Leu Glu Ser Met
    610                 615                 620
Ile Arg Leu Ser Glu Ala Met Ala Arg Met His Cys Cys Asp Glu Val
625                 630                 635                 640
Gln Pro Lys His Val Lys Glu Ala Phe Arg Leu Leu Asn Lys Ser Ile
                645                 650                 655
Ile Arg Val Glu Thr Pro Asp Val Asn Leu Asp Gln Glu Glu Glu Ile
            660                 665                 670
Gln Met Glu Val Asp Glu Gly Ala Gly Gly Ile Asn Gly His Ala Asp
        675                 680                 685
Ser Pro Ala Pro Val Asn Gly Ile Asn Gly Tyr Asn Glu Asp Ile Asn
    690                 695                 700
Gln Glu Ser Ala Pro Lys Ala Ser Leu Arg Leu Gly Phe Ser Glu Tyr
705                 710                 715                 720
Cys Arg Ile Ser Asn Leu Ile Val Leu His Leu Arg Lys Val Glu Glu
                725                 730                 735
Glu Glu Asp Glu Ser Ala Leu Lys Arg Ser Glu Leu Val Asn Trp Tyr
            740                 745                 750
Leu Lys Glu Ile Glu Ser Glu Ile Asp Ser Glu Glu Glu Leu Ile Asn
        755                 760                 765
Lys Lys Arg Ile Ile Glu Lys Val Ile His Arg Leu Thr His Tyr Asp
    770                 775                 780
His Val Leu Ile Glu Leu Thr Gln Ala Gly Leu Lys Gly Ser Thr Glu
785                 790                 795                 800
Gly Ser Glu Ser Tyr Glu Glu Asp Pro Tyr Leu Val Val Asn Pro Asn
                805                 810                 815
Tyr Leu Leu Glu Asp
            820
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<210> 130
<211> 786
<212> DNA
<213> Homo sapiens

<400> 130
cgggcgaagc agcgcgggca gcgagatgca gcaccgaggc ttcctcctcc tcaccctcct 60
cgccctgctg gcgctcacct ccgcggtcgc caaaaagaaa gataaggtga agaagggcgg 120
cccggggagc gagtgcgctg agtgggcctg ggggccctgc acccccagca gcaaggattg 180
cggcgtgggt ttccgcgagg gcacctgcgg ggcccagacc cagcgcatcc ggtgcagggt 240
gccctgcaac tggaagaagg agtttggagc cgactgcaag tacaagtttg agaactgggg 300
tgcgtgtgat gggggcacag gcaccaaagt ccgccaaggc accctgaaga aggcgcgcta 360
caatgctcag tgccaggaga ccatccgcgt caccaagccc tgcaccccca agaccaaagc 420
aaaggccaaa gccaagaaag ggaagggaaa ggactagacg ccaagcctgg atgccaagga 480
gcccctggtg tcacatgggg cctggccacg ccctccctct cccaggcccg agatgtgacc 540
caccagtgcc ttctgtctgc tcgttagctt taatcaatca tgccctgcct tgtccctctc 600
actccccagc cccaccccta agtgcccaaa gtggggaggg acaagggatt ctgggaagct 660
tgagcctccc ccaaagcaat gtgagtccca gagcccgctt ttgttcttcc ccacaattcc 720
attactaaga aacacatcaa ataaactgac tttttccccc caataaaagc tcttcttttt 780
taatat 786

<210> 131
<211> 143
<212> PRT
<213> Homo sapiens

<400> 131
Met Gln His Arg Gly Phe Leu Leu Leu Thr Leu Leu Ala Leu Leu Ala
1 5 10 15
Leu Thr Ser Ala Val Ala Lys Lys Lys Asp Lys Val Lys Lys Gly Gly
20 25 30
Pro Gly Ser Glu Cys Ala Glu Trp Ala Trp Gly Pro Cys Thr Pro Ser
35 40 45
Ser Lys Asp Cys Gly Val Gly Phe Arg Glu Gly Thr Cys Gly Ala Gln
50 55 60
Thr Gln Arg Ile Arg Cys Arg Val Pro Cys Asn Trp Lys Lys Glu Phe
65 70 75 80
Gly Ala Asp Cys Lys Tyr Lys Phe Glu Asn Trp Gly Ala Cys Asp Gly
85 90 95
Gly Thr Gly Thr Lys Val Arg Gln Gly Thr Leu Lys Lys Ala Arg Tyr
100 105 110
Asn Ala Gln Cys Gln Glu Thr Ile Arg Val Thr Lys Pro Cys Thr Pro
115 120 125
Lys Thr Lys Ala Lys Ala Lys Ala Lys Lys Gly Lys Gly Lys Asp
130 135 140

<210> 132
<211> 603
<212> DNA
<213> Homo sapiens

<400> 132
cgtgctgcta cacaagaacc ctgagactga cctgcaggac gaaaccatga agagcctgat 60
ccttcttgcc atcctggccg ccttagcggt agtaactttg tgttatgaat cacatgaaag 120
catggaatct tatgaactta atcccttcat taacaggaga aatgcaaata ccttcatatc 180
ccctcagcag agatggagag ctaaagtcca agagaggatc cgagaacgct ctaagcctgt 240
ccacgagctc aatagggaag cctgtgatga ctacagactt tgcgaacgct acgccatggt 300
ttatggatac aatgctgcct ataatcgcta cttcaggaag cgccgagggg ccaaatgaga 360
ctgagggaag aaaaaaaatc tctttttttc tggaggctgg cacctgattt tgtatccccc 420
tgtagcagca ttactgaaat acataggctt atatacaatg cttctttcct gtatattctc 480
ttgtctggct gcaccccttt ttcccgcccc cagattgata agtaatgaaa gtgcactgca 540
gtgagggtca aaggagagtc aacatatgtg attgttccat aataaacttc tggtgtgata 600
ctt 603

<210> 133
<211> 103
<212> PRT
<213> Homo sapiens

<400> 133
Met Lys Ser Leu Ile Leu Leu Ala Ile Leu Ala Ala Leu Ala Val Val
1 5 10 15
Thr Leu Cys Tyr Glu Ser His Glu Ser Met Glu Ser Tyr Glu Leu Asn
20 25 30
Pro Phe Ile Asn Arg Arg Asn Ala Asn Thr Phe Ile Ser Pro Gln Gln
35 40 45
Arg Trp Arg Ala Lys Val Gln Glu Arg Ile Arg Glu Arg Ser Lys Pro
50 55 60
Val His Glu Leu Asn Arg Glu Ala Cys Asp Asp Tyr Arg Leu Cys Glu
65 70 75 80
Arg Tyr Ala Met Val Tyr Gly Tyr Asn Ala Ala Tyr Asn Arg Tyr Phe
85 90 95
Arg Lys Arg Arg Gly Ala Lys
100

<210> 134
<211> 1778
<212> DNA
<213> Homo sapiens

<400> 134
tagaagttta caatgaagtt tcttctaata ctgctcctgc aggccactgc ttctggagct 60
cttcccctga acagctctac aagcctggaa aaaaataatg tgctatttgg tgagagatac 120
ttagaaaaat tttatggcct tgagataaac aaacttccag tgacaaaaat gaaatatagt 180
ggaaacttaa tgaaggaaaa aatccaagaa atgcagcact tcttgggtct gaaagtgacc 240
gggcaactgg acacatctac cctggagatg atgcacgcac ctcgatgtgg agtccccgat 300
ctccatcatt tcagggaaat gccagggggg cccgtatgga ggaaacatta tatcacctac 360
agaatcaata attacacacc tgacatgaac cgtgaggatg ttgactacgc aatccggaaa 420
gctttccaag tatggagtaa tgttaccccc ttgaaattca gcaagattaa cacaggcatg 480
gctgacattt tggtggtttt tgcccgtgga gctcatggag acttccatgc ttttgatggc 540
aaaggtggaa tcctagccca tgcttttgga cctggatctg gcattggagg ggatgcacat 600
ttcgatgagg acgaattctg gactacacat tcaggaggca caaacttgtt cctcactgct 660
gttcacgaga ttggccattc cttaggtctt ggccattcta gtgatccaaa ggctgtaatg 720
ttccccacct acaaatatgt cgacatcaac acatttcgcc tctctgctga tgacatacgt 780
ggcattcagt ccctgtatgg agacccaaaa gagaaccaac gcttgccaaa tcctgacaat 840
tcagaaccag ctctctgtga ccccaatttg agttttgatg ctgtcactac cgtgggaaat 900
aagatctttt tcttcaaaga caggttcttc tggctgaagg tttctgagag accaaagacc 960
agtgttaatt taatttcttc cttatggcca accttgccat ctggcattga agctgcttat 1020
gaaattgaag ccagaaatca agtttttctt tttaaagatg acaaatactg gttaattagc 1080
aatttaagac cagagccaaa ttatcccaag agcatacatt cttttggttt tcctaacttt 1140
gtgaaaaaaa ttgatgcagc tgtttttaac ccacgttttt ataggaccta cttctttgta 1200
gataaccagt attggaggta tgatgaaagg agacagatga tggaccctgg ttatcccaaa 1260
ctgattacca agaacttcca aggaatcggg cctaaaattg atgcagtctt ctattctaaa 1320
aacaaatact actatttctt ccaaggatct aaccaatttg aatatgactt cctactccaa 1380
cgtatcacca aaacactgaa aagcaatagc tggtttggtt gttagaaatg gtgtaattaa 1440
tggtttttgt tagttcactt cagcttaata agtatttatt gcatatttgc tatgtcctca 1500
gtgtaccact acttagagat atgtatcata aaaataaaat ctgtaaacca taggtaatga 1560
ttatataaaa tacataatat ttttcaattt tgaaaactct aattgtccat tcttgcttga 1620
ctctactatt aagtttgaaa atagttacct tcaaagcaag ataattctat ttgaagcatg 1680
ctctgtaagt tgcttcctaa catccttgga ctgagaaatt atacttactt ctggcataac 1740
taaaattaag tatatatatt ttggctcaaa taaaattg 1778

<210> 135
<211> 470
<212> PRT
<213> Homo sapiens

<400> 135
Met Lys Phe Leu Leu Ile Leu Leu Leu Gln Ala Thr Ala Ser Gly Ala
1 5 10 15
Leu Pro Leu Asn Ser Ser Thr Ser Leu Glu Lys Asn Asn Val Leu Phe
20 25 30
Gly Glu Arg Tyr Leu Glu Lys Phe Tyr Gly Leu Glu Ile Asn Lys Leu
35 40 45
Pro Val Thr Lys Met Lys Tyr Ser Gly Asn Leu Met Lys Glu Lys Ile
50 55 60
Gln Glu Met Gln His Phe Leu Gly Leu Lys Val Thr Gly Gln Leu Asp
65 70 75 80
Thr Ser Thr Leu Glu Met Met His Ala Pro Arg Cys Gly Val Pro Asp
85 90 95
Leu His His Phe Arg Glu Met Pro Gly Gly Pro Val Trp Arg Lys His
100 105 110
Tyr Ile Thr Tyr Arg Ile Asn Asn Tyr Thr Pro Asp Met Asn Arg Glu
115 120 125
Asp Val Asp Tyr Ala Ile Arg Lys Ala Phe Gln Val Trp Ser Asn Val
130 135 140
Thr Pro Leu Lys Phe Ser Lys Ile Asn Thr Gly Met Ala Asp Ile Leu
145 150 155 160
Val Val Phe Ala Arg Gly Ala His Gly Asp Phe His Ala Phe Asp Gly
165 170 175
Lys Gly Gly Ile Leu Ala His Ala Phe Gly Pro Gly Ser Gly Ile Gly
180 185 190
Gly Asp Ala His Phe Asp Glu Asp Glu Phe Trp Thr Thr His Ser Gly
195 200 205
Gly Thr Asn Leu Phe Leu Thr Ala Val His Glu Ile Gly His Ser Leu
210 215 220
Gly Leu Gly His Ser Ser Asp Pro Lys Ala Val Met Phe Pro Thr Tyr
225 230 235 240
Lys Tyr Val Asp Ile Asn Thr Phe Arg Leu Ser Ala Asp Asp Ile Arg
245 250 255
Gly Ile Gln Ser Leu Tyr Gly Asp Pro Lys Glu Asn Gln Arg Leu Pro
260 265 270
Asn Pro Asp Asn Ser Glu Pro Ala Leu Cys Asp Pro Asn Leu Ser Phe
275 280 285
Asp Ala Val Thr Thr Val Gly Asn Lys Ile Phe Phe Phe Lys Asp Arg
290 295 300
Phe Phe Trp Leu Lys Val Ser Glu Arg Pro Lys Thr Ser Val Asn Leu
305 310 315 320
Ile Ser Ser Leu Trp Pro Thr Leu Pro Ser Gly Ile Glu Ala Ala Tyr
325 330 335
Glu Ile Glu Ala Arg Asn Gln Val Phe Leu Phe Lys Asp Asp Lys Tyr
340 345 350
Trp Leu Ile Ser Asn Leu Arg Pro Glu Pro Asn Tyr Pro Lys Ser Ile
355 360 365
His Ser Phe Gly Phe Pro Asn Phe Val Lys Lys Ile Asp Ala Ala Val
370 375 380
Phe Asn Pro Arg Phe Tyr Arg Thr Tyr Phe Phe Val Asp Asn Gln Tyr
385 390 395 400
Trp Arg Tyr Asp Glu Arg Arg Gln Met Met Asp Pro Gly Tyr Pro Lys
405 410 415

Leu Ile Thr Lys Asn Phe Gln Gly Ile Gly Pro Lys Ile Asp Ala Val
420 425 430
Phe Tyr Ser Lys Asn Lys Tyr Tyr Tyr Phe Phe Gln Gly Ser Asn Gln
435 440 445
Phe Glu Tyr Asp Phe Leu Leu Gln Arg Ile Thr Lys Thr Leu Lys Ser
450 455 460
Asn Ser Trp Phe Gly Cys
465 470

<210> 136
<211> 1821
<212> DNA
<213> Homo sapiens

<400> 136
acaaggaggc aggcaagaca gcaaggcata gagacaacat agagctaagt aaagccagtg 60
gaaatgaaga gtcttccaat cctactgttg ctgtgcgtgg cagtttgctc agcctatcca 120
ttggatggag ctgcaagggg tgaggacacc agcatgaacc ttgttcagaa atatctagaa 180
aactactacg acctcaaaaa agatgtgaaa cagtttgtta ggagaaagga cagtggtcct 240
gttgttaaaa aaatccgaga aatgcagaag ttccttggat tggaggtgac ggggaagctg 300
gactccgaca ctctggaggt gatgcgcaag cccaggtgtg gagttcctga tgttggtcac 360
ttcagaacct ttcctggcat cccgaagtgg aggaaaaccc accttacata caggattgtg 420
aattatacac cagatttgcc aaaagatgct gttgattctg ctgttgagaa agctctgaaa 480
gtctgggaag aggtgactcc actcacattc tccaggctgt atgaaggaga ggctgatata 540
atgatctctt ttgcagttag agaacatgga gacttttacc cttttgatgg acctggaaat 600
gttttggccc atgcctatgc ccctgggcca gggattaatg gagatgccca ctttgatgat 660
gatgaacaat ggacaaagga tacaacaggg accaatttat ttctcgttgc tgctcatgaa 720
attggccact ccctgggtct ctttcactca gccaacactg aagctttgat gtacccactc 780
tatcactcac tcacagacct gactcggttc cgcctgtctc aagatgatat aaatggcatt 840
cagtccctct atggacctcc ccctgactcc cctgagaccc ccctggtacc cacggaacct 900
gtccctccag aacctgggac gccagccaac tgtgatcctg ctttgtcctt tgatgctgtc 960
agcactctga ggggagaaat cctgatcttt aaagacaggc acttttggcg caaatccctc 1020
aggaagcttg aacctgaatt gcatttgatc tcttcatttt ggccatctct tccttcaggc 1080
gtggatgccg catatgaagt tactagcaag gacctcgttt tcatttttaa aggaaatcaa 1140
ttctgggcca tcagaggaaa tgaggtacga gctggatacc caagaggcat ccacacccta 1200
ggtttccctc caaccgtgag gaaaatcgat gcagccattt ctgataagga aaagaacaaa 1260
acatatttct ttgtagagga caaatactgg agatttgatg agaagagaaa ttccatggag 1320
ccaggctttc ccaagcaaat agctgaagac tttccaggga ttgactcaaa gattgatgct 1380
gtttttgaag aatttgggtt cttttatttc tttactggat cttcacagtt ggagtttgac 1440
ccaaatgcaa agaaagtgac acacactttg aagagtaaca gctggcttaa ttgttgaaag 1500
agatatgtag aaggcacaat atgggcactt taaatgaagc taataattct tcacctaagt 1560
ctctgtgaat tgaaatgttc gttttctcct gcctgtgctg tgactcgagt cacactcaag 1620
ggaacttgag cgtgaatctg tatcttgccg gtcattttta tgttattaca gggcattcaa 1680
atgggctgct gcttagcttg caccttgtca catagagtga tctttcccaa gagaagggga 1740
agcactcgtg tgcaacagac aagtgactgt atctgtgtag actatttgct tatttaataa 1800
agacgatttg tcagttgttt t 1821

<210> 137
<211> 477
<212> PRT
<213> Homo sapiens

<400> 137
Met Lys Ser Leu Pro Ile Leu Leu Leu Leu Cys Val Ala Val Cys Ser
1 5 10 15
Ala Tyr Pro Leu Asp Gly Ala Ala Arg Gly Glu Asp Thr Ser Met Asn
20 25 30
Leu Val Gln Lys Tyr Leu Glu Asn Tyr Tyr Asp Leu Lys Lys Asp Val

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        35                  40                  45
Lys Gln Phe Val Arg Arg Lys Asp Ser Gly Pro Val Val Lys Lys Ile
    50                  55                  60
Arg Glu Met Gln Lys Phe Leu Gly Leu Glu Val Thr Gly Lys Leu Asp
65                  70                  75                  80
Ser Asp Thr Leu Glu Val Met Arg Lys Pro Arg Cys Gly Val Pro Asp
                85                  90                  95
Val Gly His Phe Arg Thr Phe Pro Gly Ile Pro Lys Trp Arg Lys Thr
            100                 105                 110
His Leu Thr Tyr Arg Ile Val Asn Tyr Thr Pro Asp Leu Pro Lys Asp
        115                 120                 125
Ala Val Asp Ser Ala Val Glu Lys Ala Leu Lys Val Trp Glu Glu Val
    130                 135                 140
Thr Pro Leu Thr Phe Ser Arg Leu Tyr Glu Gly Glu Ala Asp Ile Met
145                 150                 155                 160
Ile Ser Phe Ala Val Arg Glu His Gly Asp Phe Tyr Pro Phe Asp Gly
                165                 170                 175
Pro Gly Asn Val Leu Ala His Ala Tyr Ala Pro Gly Pro Gly Ile Asn
            180                 185                 190
Gly Asp Ala His Phe Asp Asp Asp Glu Gln Trp Thr Lys Asp Thr Thr
        195                 200                 205
Gly Thr Asn Leu Phe Leu Val Ala Ala His Glu Ile Gly His Ser Leu
    210                 215                 220
Gly Leu Phe His Ser Ala Asn Thr Glu Ala Leu Met Tyr Pro Leu Tyr
225                 230                 235                 240
His Ser Leu Thr Asp Leu Thr Arg Phe Arg Leu Ser Gln Asp Asp Ile
                245                 250                 255
Asn Gly Ile Gln Ser Leu Tyr Gly Pro Pro Pro Asp Ser Pro Glu Thr
            260                 265                 270
Pro Leu Val Pro Thr Glu Pro Val Pro Pro Glu Pro Gly Thr Pro Ala
        275                 280                 285
Asn Cys Asp Pro Ala Leu Ser Phe Asp Ala Val Ser Thr Leu Arg Gly
    290                 295                 300
Glu Ile Leu Ile Phe Lys Asp Arg His Phe Trp Arg Lys Ser Leu Arg
305                 310                 315                 320
Lys Leu Glu Pro Glu Leu His Leu Ile Ser Ser Phe Trp Pro Ser Leu
                325                 330                 335
Pro Ser Gly Val Asp Ala Ala Tyr Glu Val Thr Ser Lys Asp Leu Val
            340                 345                 350
Phe Ile Phe Lys Gly Asn Gln Phe Trp Ala Ile Arg Gly Asn Glu Val
        355                 360                 365
Arg Ala Gly Tyr Pro Arg Gly Ile His Thr Leu Gly Phe Pro Pro Thr
    370                 375                 380
Val Arg Lys Ile Asp Ala Ala Ile Ser Asp Lys Glu Lys Asn Lys Thr
385                 390                 395                 400
Tyr Phe Phe Val Glu Asp Lys Tyr Trp Arg Phe Asp Glu Lys Arg Asn
                405                 410                 415
Ser Met Glu Pro Gly Phe Pro Lys Gln Ile Ala Glu Asp Phe Pro Gly
            420                 425                 430
Ile Asp Ser Lys Ile Asp Ala Val Phe Glu Glu Phe Gly Phe Phe Tyr
        435                 440                 445
Phe Phe Thr Gly Ser Ser Gln Leu Glu Phe Asp Pro Asn Ala Lys Lys
    450                 455                 460
Val Thr His Thr Leu Lys Ser Asn Ser Trp Leu Asn Cys
465                 470                 475
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<210> 138
<211> 1127

<212> DNA
<213> Homo sapiens

<400> 138
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accaaatcaa ccataggtcc aagaacaatt gtctctggac ggcagctatg cgactcaccg 60
tgctgtgtgc tgtgtgcctg ctgcctggca gcctggccct gccgctgcct caggaggcgg 120
gaggcatgag tgagctacag tgggaacagg ctcaggacta tctcaagaga ttttatctct 180
atgactcaga aacaaaaaat gccaacagtt tagaagccaa actcaaggag atgcaaaaat 240
tctttggcct acctataact ggaatgttaa actcccgcgt catagaaata atgcagaagc 300
ccagatgtgg agtgccagat gttgcagaat actcactatt tccaaatagc ccaaaatgga 360
cttccaaagt ggtcacctac aggatcgtat catatactcg agacttaccg catattacag 420
tggatcgatt agtgtcaaag gctttaaaca tgtggggcaa agagatcccc ctgcatttca 480
ggaaagttgt atggggaact gctgacatca tgattggctt tgcgcgagga gctcatgggg 540
actcctaccc atttgatggg ccaggaaaca cgctggctca tgcctttgcg cctgggacag 600
gtctcggagg agatgctcac ttcgatgagg atgaacgctg gacggatggt agcagtctag 660
ggattaactt cctgtatgct gcaactcatg aacttggcca ttctttgggt atgggacatt 720
cctctgatcc taatgcagtg atgtatccaa cctatggaaa tggagatccc caaaatttta 780
aactttccca ggatgatatt aaaggcattc agaaactata tggaaagaga agtaattcaa 840
gaaagaaata gaaacttcag gcagaacatc cattcattca ttcattggat tgtatatcat 900
tgttgcacaa tcagaattga taagcactgt tcctccactc catttagcaa ttatgtcacc 960
ctttttattt gcagttggtt tttgaatgtc tttcactcct tttattggtt aaactccttt 1020
atggtgtgac tgtgtcttat tccatctatg agctttgtca gtgcgcgtag atgtcaataa 1080
atgttacata cacaaataaa taaaatgttt attccatggt aaattta                1127
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<210> 139
<211> 267
<212> PRT
<213> Homo sapiens

<400> 139
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Met Arg Leu Thr Val Leu Cys Ala Val Cys Leu Leu Pro Gly Ser Leu
1               5                   10                  15
Ala Leu Pro Leu Pro Gln Glu Ala Gly Gly Met Ser Glu Leu Gln Trp
            20                  25                  30
Glu Gln Ala Gln Asp Tyr Leu Lys Arg Phe Tyr Leu Tyr Asp Ser Glu
        35                  40                  45
Thr Lys Asn Ala Asn Ser Leu Glu Ala Lys Leu Lys Glu Met Gln Lys
    50                  55                  60
Phe Phe Gly Leu Pro Ile Thr Gly Met Leu Asn Ser Arg Val Ile Glu
65                  70                  75                  80
Ile Met Gln Lys Pro Arg Cys Gly Val Pro Asp Val Ala Glu Tyr Ser
                85                  90                  95
Leu Phe Pro Asn Ser Pro Lys Trp Thr Ser Lys Val Val Thr Tyr Arg
            100                 105                 110
Ile Val Ser Tyr Thr Arg Asp Leu Pro His Ile Thr Val Asp Arg Leu
        115                 120                 125
Val Ser Lys Ala Leu Asn Met Trp Gly Lys Glu Ile Pro Leu His Phe
    130                 135                 140
Arg Lys Val Val Trp Gly Thr Ala Asp Ile Met Ile Gly Phe Ala Arg
145                 150                 155                 160
Gly Ala His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Gly Asn Thr Leu
                165                 170                 175
Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe
            180                 185                 190
Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe
        195                 200                 205
Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His
    210                 215                 220
Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp
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225 230 235 240
Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys
245 250 255
Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys
260 265

<210> 140
<211> 1078
<212> DNA
<213> Homo sapiens

<400> 140
aagaacaatt gtctctggac ggcagctatg cgactcaccg tgctgtgtgc tgtgtgcctg 60
ctgcctggca gcctggccct gccgctgcct caggaggcgg gaggcatgag tgagctacag 120
tgggaacagg ctcaggacta tctcaagaga ttttatctct atgactcaga aacaaaaaat 180
gccaacagtt tagaagccaa actcaaggag atgcaaaaat tctttggcct acctataact 240
ggaatgttaa actcccgcgt catagaaata atgcagaagc ccagatgtgg agtgccagat 300
gttgcagaat actcactatt tccaaatagc ccaaaatgga cttccaaagt ggtcacctac 360
aggatcgtat catatactcg agacttaccg catattacag tggatcgatt agtgtcaaag 420
gctttaaaca tgtggggcaa agagatcccc ctgcatttca ggaaagttgt atggggaact 480
gctgacatca tgattggctt tgcgcgagga gctcatgggg actcctaccc atttgatggg 540
ccaggaaaca cgctggctca tgcctttgcg cctgggacag gtctcggagg agatgctcac 600
ttcgatgagg atgaacgctg gacggatggt agcagtctag ggattaactt cctgtatgct 660
gcaactcatg aacttggcca ttctttgggt atgggacatt cctctgatcc taatgcagtg 720
atgtatccaa cctatggaaa tggagatccc caaaatttta aactttccca ggatgatatt 780
aaaggcattc agaaactata tggaaagaga agtaattcaa gaaagaaata gaaacttcag 840
gcagaacatc cattcattca ttcattggat tgtatatcat tgttgcacaa tcagaattga 900
taagcactgt tcctccactc catttagcaa ttatgtcacc ctttttttatt gcagttggtt 960
tttgaatgtc tttcactcct tttattggtt aaactccttt atggtgtgac tgtgtcttat 1020
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<210> 141
<211> 2334
<212> DNA
<213> Homo sapiens

<400> 141
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cctgagaacc aatctcaccg acaggcagct ggcagaggaa tacctgtacc gctatggtta 180
cactcgggtg gcagagatgc gtggagagtc gaaatctctg gggcctgcgc tgctgcttct 240
ccagaagcaa ctgtccctgc ccgagaccgg tgagctggat agcgccacgc tgaaggccat 300
gcgaacccca cggtgcgggg tcccagacct gggcagattc caaacctttg agggcgacct 360
caagtggcac caccacaaca tcacctattg gatccaaaac tactcggaag acttgccgcg 420
ggcggtgatt gacgacgcct ttgcccgcgc cttcgcactg tggagcgcgg tgacgccgct 480
caccttcact cgcgtgtaca gccgggacgc agacatcgtc atccagtttg gtgtcgcgga 540
gcacggagac gggtatccct tcgacgggaa ggacgggctc ctggcacacg cctttcctcc 600
tggccccggc attcagggag acgcccattt cgacgatgac gagttgtggt ccctgggcaa 660
gggcgtcgtg gttccaactc ggtttggaaa cgcagatggc gcggcctgcc acttcccctt 720
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ctggtgcagt accacggcca actacgacac cgacgaccgg tttggcttct gccccagcga 840
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cgccaccacc gccaactacg accgggacaa gctcttcggc ttctgcccga cccgagctga 1020
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ccccggggtg cctttggaca cgcacgacgt cttccagtac cgagagaaag cctatttctg 2040
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gcagtgccat gtaaatcccc actgggacca accctgggga aggagccagt ttgccggata 2220
caaactggta ttctgttctg gaggaaaggg aggagtggag gtgggctggg ccctctcttc 2280
tcacctttgt tttttgttgg agtgtttcta ataaacttgg attctctaac cttt       2334
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<210> 142
<211> 707
<212> PRT
<213> Homo sapiens

<400> 142

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Met Ser Leu Trp Gln Pro Leu Val Leu Val Leu Leu Val Leu Gly Cys
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Cys Phe Ala Ala Pro Arg Gln Arg Gln Ser Thr Leu Val Leu Phe Pro
            20                  25                  30
Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr
        35                  40                  45
Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser
    50                  55                  60
Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser Leu
65                  70                  75                  80
Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr
                85                  90                  95
Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly
            100                 105                 110
Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn Tyr
        115                 120                 125
Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg Ala
    130                 135                 140
Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr
145                 150                 155                 160
Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His Gly
                165                 170                 175
Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe
            180                 185                 190
Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp Glu
        195                 200                 205
Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly Asn
    210                 215                 220
Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu Gly Arg Ser
225                 230                 235                 240
Tyr Ser Ala Cys Thr Thr Asp Gly Arg Ser Asp Gly Leu Pro Trp Cys
                245                 250                 255
Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly Phe Cys Pro
            260                 265                 270
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Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro Cys
        275                 280                 285
Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr Thr
    290                 295                 300
Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn Tyr
305                 310                 315                 320
Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser Thr
                325                 330                 335
Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe Thr
            340                 345                 350
Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly Asp
        355                 360                 365
Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys Lys
    370                 375                 380
Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala Ala
385                 390                 395                 400
His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu
                405                 410                 415
Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His
            420                 425                 430
Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu
        435                 440                 445
Pro Glu Pro Arg Pro Pro Thr Thr Thr Thr Pro Gln Pro Thr Ala Pro
    450                 455                 460
Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg
465                 470                 475                 480
Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro
                485                 490                 495
Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro Val
            500                 505                 510
Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly
        515                 520                 525
Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu
    530                 535                 540
Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp
545                 550                 555                 560
Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu Ser
                565                 570                 575
Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly
            580                 585                 590
Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala
        595                 600                 605
Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met
    610                 615                 620
Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln
625                 630                 635                 640
Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly
                645                 650                 655
Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr
            660                 665                 670
Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu
        675                 680                 685
Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile Leu Gln Cys
    690                 695                 700
Pro Glu Asp
705
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<210> 143

<211> 2217
<212> DNA
<213> Homo sapiens

<400> 143
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cctccctccc tgggatctac acagaccatg gccttgccaa cggctcgacc cctgttgggg 120
tcctgtggga cccccgccct cggcagcctc ctgttcctgc tcttcagcct cggatgggtg 180
cagccctcga ggaccctggc tggagagaca gggcaggagg ctgcacccct ggacggagtc 240
ctggccaacc cacctaacat ttccagcctc tcccctcgcc aactccttgg cttcccgtgt 300
gcggaggtgt ccggcctgag cacggagcgt gtccgggagc tggctgtggc cttggcacag 360
aagaatgtca agctctcaac agagcagctg cgctgtctgg ctcaccggct ctctgagccc 420
cccgaggacc tggacgccct cccattggac ctgctgctat tcctcaaccc agatgcgttc 480
tcggggcccc aggcctgcac ccgtttcttc tcccgcatca cgaaggccaa tgtggacctg 540
ctcccgaggg ggctcccgga gcgacagcgg ctgctgcctg cggctctggc ctgctggggt 600
gtgcgggggt ctctgctgag cgaggctgat gtgcgggctc tgggaggcct ggcttgcgac 660
ctgcctgggc gctttgtggc cgagtcggcc gaagtgctgc taccccggct ggtgagctgc 720
ccgggacccc tggaccagga ccagcaggag gcagccaggg cggctctgca gggcggggga 780
ccccccctacg gcccccgtc gacatggtct gtctccacga tggacgctct gcggggcctg 840
ctgcccgtgc tgggccagcc catcatccgc agcatcccgc agggcatcgt ggccgcgtgg 900
cggcaacgct cctctcggga cccatcctgg cggcagcctg aacggaccat cctccggccg 960
cggttccggc gggaagtgga gaagacagcc tgtccttcag gcaagaaggc ccgcgagata 1020
gacgagagcc tcatcttcta caagaagtgg gagctggaag cctgcgtgga tgcggccctg 1080
ctggccaccc agatggaccg cgtgaacgcc atccccttca cctacgagca gctggacgtc 1140
ctaaagcata aactggatga gctctaccca caaggttacc ccgagtctgt gatccagcac 1200
ctgggctacc tcttcctcaa gatgagccct gaggacattc gcaagtggaa tgtgacgtcc 1260
ctggagaccc tgaaggcttt gcttgaagtc aacaaagggc acgaaatgag tcctcaggct 1320
cctcggcggc ccctcccaca ggtggccacc ctgatcgacc gctttgtgaa gggaaggggc 1380
cagctagaca aagacaccct agacaccctg accgccttct accctgggta cctgtgctcc 1440
ctcagccccg aggagctgag ctccgtgccc cccagcagca tctgggcggt caggccccag 1500
gacctggaca cgtgtgaccc aaggcagctg gacgtcctct atcccaaggc ccgccttgct 1560
ttccagaaca tgaacgggtc cgaatacttc gtgaagatcc agtccttcct gggtggggcc 1620
cccacggagg atttgaaggc gctcagtcag cagaatgtga gcatggactt ggccacgttc 1680
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ctacggcagc ggcaggacga cctggacacg ctggggctgg ggctacaggg cggcatcccc 1860
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tccccgcctg gccaggagca ggcacgggtg atccccgttc caccccaaga gaactcgcgc 2160
tcagtaaacg ggaacatgcc ccctgcagac acgtaaaaaa aaaaaaaaaa aaaaaaa 2217

<210> 144
<211> 702
<212> PRT
<213> Homo sapiens

<400> 144
Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
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Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
20 25 30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
35 40 45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
50 55 60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65 70 75 80

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Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
                85                  90                  95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
    130                 135                 140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
    210                 215                 220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
            260                 265                 270
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
        275                 280                 285
Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
    290                 295                 300
Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320
Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
                325                 330                 335
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380
Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385                 390                 395                 400
Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu
                405                 410                 415
Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
            420                 425                 430
Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
        435                 440                 445
Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
    450                 455                 460
Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
465                 470                 475                 480
Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
                485                 490                 495
Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
            500                 505                 510
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
        515                 520                 525
Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
    530                 535                 540
Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala
```

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545                 550                 555                 560
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
                565                 570                 575
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
            580                 585                 590
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Gly Gly Arg Gly Gly Gln
        595                 600                 605
Ala Arg Ala Gly Gly Arg Ala Gly Gly Val Glu Val Gly Ala Leu Ser
    610                 615                 620
His Pro Ser Leu Cys Arg Gly Pro Leu Gly Asp Ala Leu Pro Pro Arg
625                 630                 635                 640
Thr Trp Thr Cys Ser His Arg Pro Gly Thr Ala Pro Ser Leu His Pro
                645                 650                 655
Gly Leu Arg Ala Pro Leu Pro Cys Trp Pro Gln Pro Cys Trp Gly Ser
            660                 665                 670
Pro Pro Gly Gln Glu Gln Ala Arg Val Ile Pro Val Pro Pro Gln Glu
        675                 680                 685
Asn Ser Arg Ser Val Asn Gly Asn Met Pro Pro Ala Asp Thr
    690                 695                 700
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<210> 145
<211> 2135
<212> DNA
<213> Homo sapiens

<400> 145

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tcctgtggga cccccgccct cggcagcctc ctgttcctgc tcttcagcct cggatgggtg 180
cagccctcga ggaccctggc tggagagaca gggcaggagg ctgcacccct ggacggagtc 240
ctggccaacc cacctaacat ttccagcctc tcccctcgcc aactccttgg cttcccgtgt 300
gcggaggtgt ccggcctgag cacggagcgt gtccgggagc tggctgtggc cttggcacag 360
aagaatgtca agctctcaac agagcagctg cgctgtctgg ctcaccggct ctctgagccc 420
cccgaggacc tggacgccct cccattggac ctgctgctat tcctcaaccc agatgcgttc 480
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ctcccgaggg gggctcccga gcgacagcgg ctgctgcctg cggctctggc ctgctggggt 600
gtgcgggggt ctctgctgag cgaggctgat gtgcgggctc tgggaggcct ggcttgcgac 660
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ccgggacccc tggaccagga ccagcaggag gcagccaggg cggctctgca gggcggggga 780
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cggttccggc gggaagtgga gaagacagcc tgtccttcag gcaagaaggc ccgcgagata 1020
gacgagagcc tcatcttcta caagaagtgg gagctggaag cctgcgtgga tgcggccctg 1080
ctggccaccc agatggaccg cgtgaacgcc atccccttca cctacgagca gctggacgtc 1140
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ctgggctacc tcttcctcaa gatgagccct gaggacattc gcaagtggaa tgtgacgtcc 1260
ctggagaccc tgaaggcttt gcttgaagtc aacaaagggc acgaaatgag tcctcaggct 1320
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gacctggaca cgtgtgaccc aaggcagctg gacgtcctct atcccaaggc ccgccttgct 1560
ttccagaaca tgaacgggtc cgaatacttc gtgaagatcc agtccttcct gggtggggcc 1620
cccacggagg atttgaaggc gctcagtcag cagaatgtga gcatggactt ggccacgttc 1680
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ctacggcagc ggcaggacga cctggacacg ctggggctgg ggctacaggg cggcatcccc 1860
aacggctacc tggtcctaga cctcagcgtg caagaggccc tctcggggac gccctgcctc 1920
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ctaggacctg gacctgttct caccgtcctg gcactgctcc tagcctccac cctggcctga 1980
gggccccact cccttgctgg ccccagccct gctggggatc cccgcctggc caggagcagg 2040
cacgggtgat ccccgttcca ccccaagaga actcgcgctc agtaaacggg aacatgcccc 2100
ctgcagacac gtaaaaaaaa aaaaaaaaaa aaaaa                            2135

<210> 146
<211> 630
<212> PRT
<213> Homo sapiens

<400> 146
Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
 1               5                  10                  15
Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
            20                  25                  30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
        35                  40                  45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
    50                  55                  60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65                  70                  75                  80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
                85                  90                  95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
    130                 135                 140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
    210                 215                 220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
            260                 265                 270
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
        275                 280                 285
Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
    290                 295                 300
Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320
Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
                325                 330                 335
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380
```

Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385 390 395 400
Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu
405 410 415
Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
420 425 430
Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
435 440 445
Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
450 455 460
Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
465 470 475 480
Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
485 490 495
Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
500 505 510
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
515 520 525
Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
530 535 540
Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala
545 550 555 560
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
565 570 575
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
580 585 590
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Glu Ala Leu Ser Gly Thr
595 600 605
Pro Cys Leu Leu Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu
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Leu Ala Ser Thr Leu Ala
625 630

<210> 147
<211> 2105
<212> DNA
<213> Homo sapiens

<400> 147
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tcctgtggga cccccgccct cggcagcctc ctgttcctgc tcttcagcct cggatgggtg 180
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gcggaggtgt ccggcctgag cacggagcgt gtccgggagc tggctgtggc cttggcacag 360
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ctcccgaggg gggctcccga gcgacagcgg ctgctgcctg cggctctggc ctgctggggt 600
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gctggggatc cccgcctggc caggagcagg cacgggtgat ccccgttcca ccccaagaga 2040
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aaaaa 2105

<210> 148
<211> 620
<212> PRT
<213> Homo sapiens

<400> 148
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Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
35 40 45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
50 55 60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65 70 75 80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
85 90 95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
100 105 110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
115 120 125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
130 135 140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145 150 155 160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
165 170 175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
180 185 190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
195 200 205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
210 215 220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225 230 235 240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
245 250 255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
260 265 270
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile

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        275                 280                 285
Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
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Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320
Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
                325                 330                 335
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380
Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385                 390                 395                 400
Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu
                405                 410                 415
Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
            420                 425                 430
Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
        435                 440                 445
Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
    450                 455                 460
Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
465                 470                 475                 480
Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
                485                 490                 495
Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
            500                 505                 510
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
        515                 520                 525
Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
    530                 535                 540
Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala
545                 550                 555                 560
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
                565                 570                 575
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
            580                 585                 590
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Gly Pro Gly Pro Val Leu
        595                 600                 605
Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala
    610                 615                 620
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<210> 149
<211> 2193
<212> DNA
<213> Homo sapiens

<400> 149

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tcctgtggga cccccgccct cggcagcctc ctgttcctgc tcttcagcct cggatgggtg 180
cagccctcga ggaccctggc tggagagaca gggcaggagg ctgcacccct ggacggagtc 240
ctggccaacc cacctaacat ttccagcctc tcccctcgcc aactccttgg cttcccgtgt 300
gcggaggtgt ccggcctgag cacggagcgt gtccgggagc tggctgtggc cttggcacag 360
aagaatgtca agctctcaac agagcagctg cgctgtctgg ctcaccggct ctctgagccc 420
cccgaggacc tggacgccct cccattggac ctgctgctat tcctcaaccc agatgcgttc 480
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tcggggcccc aggcctgcac ccgtttcttc tcccgcatca cgaaggccaa tgtggacctg 540
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gcagacacgt aaaaaaaaaa aaaaaaaaaa aaa 2193

<210> 150
<211> 694
<212> PRT
<213> Homo sapiens

<400> 150
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Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
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Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
35 40 45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
50 55 60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65 70 75 80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
85 90 95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
100 105 110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
115 120 125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
130 135 140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145 150 155 160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
165 170 175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu

180 185 190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
195 200 205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
210 215 220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225 230 235 240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
245 250 255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
260 265 270
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
275 280 285
Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
290 295 300
Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305 310 315 320
Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
325 330 335
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
340 345 350
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
355 360 365
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
370 375 380
Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385 390 395 400
Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp
405 410 415
Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
420 425 430
Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
435 440 445
Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp
450 455 460
Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
465 470 475 480
Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
485 490 495
Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
500 505 510
Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
515 520 525
Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
530 535 540
Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
545 550 555 560
Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
565 570 575
Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
580 585 590
Val Gln Gly Gly Arg Gly Gly Gln Ala Arg Ala Gly Gly Arg Ala Gly
595 600 605
Gly Val Glu Val Gly Ala Leu Ser His Pro Ser Leu Cys Arg Gly Pro
610 615 620
Leu Gly Asp Ala Leu Pro Pro Arg Thr Trp Thr Cys Ser His Arg Pro
625 630 635 640
Gly Thr Ala Pro Ser Leu His Pro Gly Leu Arg Ala Pro Leu Pro Cys
645 650 655

Trp Pro Gln Pro Cys Trp Gly Ser Pro Pro Gly Gln Glu Gln Ala Arg
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Val Ile Pro Val Pro Pro Gln Glu Asn Ser Arg Ser Val Asn Gly Asn
675 680 685
Met Pro Pro Ala Asp Thr
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<210> 151
<211> 2081
<212> DNA
<213> Homo sapiens

<400> 151
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tgccccctgc agacacgtaa aaaaaaaaaa aaaaaaaaaa a 2081

<210> 152
<211> 612
<212> PRT
<213> Homo sapiens

<400> 152
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Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln

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Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
35 40 45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
50 55 60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65 70 75 80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
85 90 95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
100 105 110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
115 120 125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
130 135 140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145 150 155 160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
165 170 175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
180 185 190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
195 200 205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
210 215 220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225 230 235 240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
245 250 255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
260 265 270
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
275 280 285
Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
290 295 300
Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305 310 315 320
Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
325 330 335
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
340 345 350
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
355 360 365
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
370 375 380
Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385 390 395 400
Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp
405 410 415
Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
420 425 430
Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
435 440 445
Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp
450 455 460
Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
465 470 475 480
Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
485 490 495

Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
500 505 510
Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
515 520 525
Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
530 535 540
Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
545 550 555 560
Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
565 570 575
Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
580 585 590
Val Gln Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu Leu Ala
595 600 605
Ser Thr Leu Ala
610

<210> 153
<211> 2111
<212> DNA
<213> Homo sapiens

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tcctgtggga cccccgccct cggcagcctc ctgttcctgc tcttcagcct cggatgggtg 180
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aaaaaaaaaa a 2111

<210> 154
<211> 622
<212> PRT
<213> Homo sapiens

<400> 154
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Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
35 40 45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
50 55 60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65 70 75 80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
85 90 95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
100 105 110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
115 120 125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
130 135 140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145 150 155 160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
165 170 175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
180 185 190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
195 200 205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
210 215 220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225 230 235 240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
245 250 255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
260 265 270
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
275 280 285
Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
290 295 300
Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305 310 315 320
Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
325 330 335
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
340 345 350
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
355 360 365
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
370 375 380
Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385 390 395 400
Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp

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Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
            420                 425                 430
Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
        435                 440                 445
Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp
    450                 455                 460
Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
465                 470                 475                 480
Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
                485                 490                 495
Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
            500                 505                 510
Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
        515                 520                 525
Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
    530                 535                 540
Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
545                 550                 555                 560
Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
                565                 570                 575
Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
            580                 585                 590
Val Gln Glu Ala Leu Ser Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro
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Val Leu Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala
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<210> 155
<211> 1721
<212> DNA
<213> Homo sapiens

<400> 155

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agaagttcag tgcccagctc tactgagaag aatgctgtga gtatgaccag cagcgtactc 240
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gctgtctgtc agtgccgccg aaagaactac gggcagctgg acatctttcc agcccgggat 1440
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ctgggagccc ccaccacaac acttcccagg catggaattc c 1721

<210> 156
<211> 515
<212> PRT
<213> Homo sapiens

<400> 156
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Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
35 40 45
Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His
50 55 60
Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu
65 70 75 80
Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln
85 90 95
Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr
100 105 110
Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro
115 120 125
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
130 135 140
Arg Pro Pro Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
145 150 155 160
Ala Pro Asp Thr Arg Pro Pro Pro Gly Ser Thr Ala Pro Ala Ala His
165 170 175
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
180 185 190
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala Leu
195 200 205
Ala Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly Ser
210 215 220
Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala Arg
225 230 235 240
Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro Ser
245 250 255
His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys Thr
260 265 270
Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser Ser
275 280 285
Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe Phe
290 295 300
Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp
305 310 315 320
Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met
325 330 335
Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile
340 345 350
Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg
355 360 365
Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr

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Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser
385                 390                 395                 400
Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val
                405                 410                 415
Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala
            420                 425                 430
Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg
        435                 440                 445
Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His
    450                 455                 460
Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro
465                 470                 475                 480
Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn
                485                 490                 495
Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser
            500                 505                 510
Ala Asn Leu
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<210> 157
<211> 4139
<212> DNA
<213> Homo sapiens

<400> 157
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<210> 158
<211> 1255
<212> PRT
<213> Homo sapiens

<400> 158
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20 25 30
Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
35 40 45
Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His
50 55 60
Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu
65 70 75 80
Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln
85 90 95
Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr
100 105 110
Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro

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    130                 135                 140
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
145                 150                 155                 160
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
                165                 170                 175
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
            180                 185                 190
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
        195                 200                 205
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
    210                 215                 220
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
225                 230                 235                 240
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
                245                 250                 255
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
            260                 265                 270
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
        275                 280                 285
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
    290                 295                 300
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
305                 310                 315                 320
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
                325                 330                 335
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
            340                 345                 350
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
        355                 360                 365
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
    370                 375                 380
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
385                 390                 395                 400
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
                405                 410                 415
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
            420                 425                 430
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
        435                 440                 445
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
    450                 455                 460
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
465                 470                 475                 480
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
                485                 490                 495
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
            500                 505                 510
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
        515                 520                 525
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
    530                 535                 540
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
545                 550                 555                 560
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
                565                 570                 575
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
            580                 585                 590
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Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
595 600 605
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
610 615 620
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
625 630 635 640
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
645 650 655
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
660 665 670
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
675 680 685
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
690 695 700
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
705 710 715 720
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
725 730 735
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
740 745 750
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
755 760 765
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
770 775 780
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
785 790 795 800
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
805 810 815
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
820 825 830
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
835 840 845
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
850 855 860
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
865 870 875 880
Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His
885 890 895
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
900 905 910
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro
915 920 925
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn
930 935 940
Arg Pro Ala Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser
945 950 955 960
Ala Ser Gly Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly
965 970 975
Thr Ser Ala Arg Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe
980 985 990
Ser Ile Pro Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His
995 1000 1005
Ser Thr Lys Thr Asp Ala Ser Ser Thr His His Ser Ser Val Pro Pro
1010 1015 1020
Leu Thr Ser Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val
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Gln Ala Ser Met Pro Asp Asn Thr Ala Ala Gln Lys Val Cys His Leu
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Met Gly Ile Asn Val Thr Asp Phe Thr Arg Ser Ile Leu Thr Pro Arg
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Pro Gly Val Leu Ala Leu Leu Asp Glu Glu Cys Trp Phe Pro Lys Ala
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Lys Leu Asp Ala Phe Leu Val Leu Glu Gln Leu Arg Cys Asn Gly Val
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Glu Glu Thr Arg Ser His Glu Ala Gln Val Gln Glu Met Arg Gln Lys
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His Ala Gln Ala Val Glu Glu Leu Thr Glu Gln Leu Glu Gln Phe Lys
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Gln Ser Lys Cys Ser Asp Gly Glu Arg Ala Arg Ala Glu Leu Asn Asp
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Gln Val Glu Asp Glu Arg Lys Met Ala Glu Gln Tyr Lys Glu Gln Ala
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Glu Lys Gly Asn Ala Arg Val Lys Gln Leu Lys Arg Gln Leu Glu Glu
        1875                1880                1885
Ala Glu Glu Glu Ser Gln Arg Ile Asn Ala Asn Arg Arg Lys Leu Gln
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Arg Glu Leu Asp Glu Ala Thr Glu Ser Asn Glu Ala Met Gly Arg Glu
1905                1910                1915                1920
Val Asn Ala Leu Lys Ser Lys Leu Arg Arg Gly Asn Glu Thr Ser Phe
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Val Pro Ser Arg Arg Ser Gly Gly Arg Arg Val Ile Glu Asn Ala Asp
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<210> 163
<211> 6900
<212> DNA
<213> Homo sapiens

<400> 163

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<210> 164
<211> 1938
<212> PRT
<213> Homo sapiens

<400> 164

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Lys Lys Arg His Glu Met Pro Pro His Ile Tyr Ala Ile Ala Asp Thr
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Thr Gly Glu Ser Gly Ala Gly Lys Thr Glu Asn Thr Lys Lys Val Ile
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Gln Tyr Leu Ala Val Val Ala Ser Ser His Lys Gly Lys Lys Asp Thr
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        355                 360                 365
Gln Ala Ser Met Pro Asp Asn Thr Ala Ala Gln Lys Val Cys His Leu
    370                 375                 380
Met Gly Ile Asn Val Thr Asp Phe Thr Arg Ser Ile Leu Thr Pro Arg
385                 390                 395                 400
Ile Lys Val Gly Arg Asp Val Val Gln Lys Ala Gln Thr Lys Glu Gln
                405                 410                 415
Ala Asp Phe Ala Val Glu Ala Leu Ala Lys Ala Thr Tyr Glu Arg Leu
            420                 425                 430
Phe Arg Trp Ile Leu Thr Arg Val Asn Lys Ala Leu Asp Lys Thr His
        435                 440                 445
Arg Gln Gly Ala Ser Phe Leu Gly Ile Leu Asp Ile Ala Gly Phe Glu
    450                 455                 460
Ile Phe Glu Val Asn Ser Phe Glu Gln Leu Cys Ile Asn Tyr Thr Asn
465                 470                 475                 480
Glu Lys Leu Gln Gln Leu Phe Asn His Thr Met Phe Ile Leu Glu Gln
                485                 490                 495
Glu Glu Tyr Gln Arg Glu Gly Ile Glu Trp Asn Phe Ile Asp Phe Gly
            500                 505                 510
Leu Asp Leu Gln Pro Cys Ile Glu Leu Ile Glu Arg Pro Asn Asn Pro
        515                 520                 525
Pro Gly Val Leu Ala Leu Leu Asp Glu Glu Cys Trp Phe Pro Lys Ala
    530                 535                 540
Thr Asp Lys Ser Phe Val Glu Lys Leu Cys Thr Glu Gln Gly Ser His
545                 550                 555                 560
Pro Lys Phe Gln Lys Pro Lys Gln Leu Lys Asp Lys Thr Glu Phe Ser
                565                 570                 575
Ile Ile His Tyr Ala Gly Lys Val Asp Tyr Asn Ala Ser Ala Trp Leu
            580                 585                 590
Thr Lys Asn Met Asp Pro Leu Asn Asp Asn Val Thr Ser Leu Leu Asn
        595                 600                 605
Ala Ser Ser Asp Lys Phe Val Ala Asp Leu Trp Lys Asp Val Asp Arg
    610                 615                 620
Ile Val Gly Leu Asp Gln Met Ala Lys Met Thr Glu Ser Ser Leu Pro
625                 630                 635                 640
Ser Ala Ser Lys Thr Lys Lys Gly Met Phe Arg Thr Val Gly Gln Leu
                645                 650                 655
Tyr Lys Glu Gln Leu Gly Lys Leu Met Thr Thr Leu Arg Asn Thr Thr
            660                 665                 670
Pro Asn Phe Val Arg Cys Ile Ile Pro Asn His Glu Lys Arg Ser Gly
        675                 680                 685
```

Lys Leu Asp Ala Phe Leu Val Leu Glu Gln Leu Arg Cys Asn Gly Val
690 695 700
Leu Glu Gly Ile Arg Ile Cys Arg Gln Gly Phe Pro Asn Arg Ile Val
705 710 715 720
Phe Gln Glu Phe Arg Gln Arg Tyr Glu Ile Leu Ala Ala Asn Ala Ile
725 730 735
Pro Lys Gly Phe Met Asp Gly Lys Gln Ala Cys Ile Leu Met Ile Lys
740 745 750
Ala Leu Glu Leu Asp Pro Asn Leu Tyr Arg Ile Gly Gln Ser Lys Ile
755 760 765
Phe Phe Arg Thr Gly Val Leu Ala His Leu Glu Glu Glu Arg Asp Leu
770 775 780
Lys Ile Thr Asp Val Ile Met Ala Phe Gln Ala Met Cys Arg Gly Tyr
785 790 795 800
Leu Ala Arg Lys Ala Phe Ala Lys Arg Gln Gln Gln Leu Thr Ala Met
805 810 815
Lys Val Ile Gln Arg Asn Cys Ala Ala Tyr Leu Lys Leu Arg Asn Trp
820 825 830
Gln Trp Trp Arg Leu Phe Thr Lys Val Lys Pro Leu Leu Gln Val Thr
835 840 845
Arg Gln Glu Glu Glu Met Gln Ala Lys Glu Asp Glu Leu Gln Lys Thr
850 855 860
Lys Glu Arg Gln Gln Lys Ala Glu Asn Glu Leu Lys Glu Leu Glu Gln
865 870 875 880
Lys His Ser Gln Leu Thr Glu Glu Lys Asn Leu Leu Gln Glu Gln Leu
885 890 895
Gln Ala Glu Thr Glu Leu Tyr Ala Glu Ala Glu Glu Met Arg Val Arg
900 905 910
Leu Ala Ala Lys Lys Gln Glu Leu Glu Glu Ile Leu His Glu Met Glu
915 920 925
Ala Arg Leu Glu Glu Glu Glu Asp Arg Gly Gln Gln Leu Gln Ala Glu
930 935 940
Arg Lys Lys Met Ala Gln Gln Met Leu Asp Leu Glu Glu Gln Leu Glu
945 950 955 960
Glu Glu Glu Ala Ala Arg Gln Lys Leu Gln Leu Glu Lys Val Thr Ala
965 970 975
Glu Ala Lys Ile Lys Lys Leu Glu Asp Glu Ile Leu Val Met Asp Asp
980 985 990
Gln Asn Asn Lys Leu Ser Lys Glu Arg Lys Leu Leu Glu Glu Arg Ile
995 1000 1005
Ser Asp Leu Thr Thr Asn Leu Ala Glu Glu Glu Glu Lys Ala Lys Asn
1010 1015 1020
Leu Thr Lys Leu Lys Asn Lys His Glu Ser Met Ile Ser Glu Leu Glu
1025 1030 1035 1040
Val Arg Leu Lys Lys Glu Glu Lys Ser Arg Gln Glu Leu Glu Lys Leu
1045 1050 1055
Lys Arg Lys Leu Glu Gly Asp Ala Ser Asp Phe His Glu Gln Ile Ala
1060 1065 1070
Asp Leu Gln Ala Gln Ile Ala Glu Leu Lys Met Gln Leu Ala Lys Lys
1075 1080 1085
Glu Glu Glu Leu Gln Ala Ala Leu Ala Arg Leu Asp Asp Glu Ile Ala
1090 1095 1100
Gln Lys Asn Asn Ala Leu Lys Lys Ile Arg Glu Leu Glu Gly His Ile
1105 1110 1115 1120
Ser Asp Leu Gln Glu Asp Leu Asp Ser Glu Arg Ala Ala Arg Asn Lys
1125 1130 1135
Ala Glu Lys Gln Lys Arg Asp Leu Gly Glu Glu Leu Glu Ala Leu Lys
1140 1145 1150
Thr Glu Leu Glu Asp Thr Leu Asp Ser Thr Ala Thr Gln Gln Glu Leu

```
        1155                1160                1165
Arg Ala Lys Arg Glu Gln Glu Val Thr Val Leu Lys Lys Ala Leu Asp
    1170                1175                1180
Glu Glu Thr Arg Ser His Glu Ala Gln Val Gln Glu Met Arg Gln Lys
1185                1190                1195                1200
His Ala Gln Ala Val Glu Glu Leu Thr Glu Gln Leu Glu Gln Phe Lys
                1205                1210                1215
Arg Ala Lys Ala Asn Leu Asp Lys Asn Lys Gln Thr Leu Glu Lys Glu
            1220                1225                1230
Asn Ala Asp Leu Ala Gly Glu Leu Arg Val Leu Gly Gln Ala Lys Gln
        1235                1240                1245
Glu Val Glu His Lys Lys Lys Lys Leu Glu Ala Gln Val Gln Glu Leu
    1250                1255                1260
Gln Ser Lys Cys Ser Asp Gly Glu Arg Ala Arg Ala Glu Leu Asn Asp
1265                1270                1275                1280
Lys Val His Lys Leu Gln Asn Glu Val Glu Ser Val Thr Gly Met Leu
                1285                1290                1295
Asn Glu Ala Glu Gly Lys Ala Ile Lys Leu Ala Lys Asp Val Ala Ser
            1300                1305                1310
Leu Ser Ser Gln Leu Gln Asp Thr Gln Glu Leu Leu Gln Glu Glu Thr
        1315                1320                1325
Arg Gln Lys Leu Asn Val Ser Thr Lys Leu Arg Gln Leu Glu Glu Glu
    1330                1335                1340
Arg Asn Ser Leu Gln Asp Gln Leu Asp Glu Glu Met Glu Ala Lys Gln
1345                1350                1355                1360
Asn Leu Glu Arg His Ile Ser Thr Leu Asn Ile Gln Leu Ser Asp Ser
                1365                1370                1375
Lys Lys Lys Leu Gln Asp Phe Ala Ser Thr Val Glu Ala Leu Glu Glu
            1380                1385                1390
Gly Lys Lys Arg Phe Gln Lys Glu Ile Glu Asn Leu Thr Gln Gln Tyr
        1395                1400                1405
Glu Glu Lys Ala Ala Ala Tyr Asp Lys Leu Glu Lys Thr Lys Asn Arg
    1410                1415                1420
Leu Gln Gln Glu Leu Asp Asp Leu Val Val Asp Leu Asp Asn Gln Arg
1425                1430                1435                1440
Gln Leu Val Ser Asn Leu Glu Lys Lys Gln Arg Lys Phe Asp Gln Leu
                1445                1450                1455
Leu Ala Glu Glu Lys Asn Ile Ser Ser Lys Tyr Ala Asp Glu Arg Asp
            1460                1465                1470
Arg Ala Glu Ala Glu Ala Arg Glu Lys Glu Thr Lys Ala Leu Ser Leu
        1475                1480                1485
Ala Arg Ala Leu Glu Glu Ala Leu Glu Ala Lys Glu Glu Leu Glu Arg
    1490                1495                1500
Thr Asn Lys Met Leu Lys Ala Glu Met Glu Asp Leu Val Ser Ser Lys
1505                1510                1515                1520
Asp Asp Val Gly Lys Asn Val His Glu Leu Glu Lys Ser Lys Arg Ala
                1525                1530                1535
Leu Glu Thr Gln Met Glu Glu Met Lys Thr Gln Leu Glu Glu Leu Glu
            1540                1545                1550
Asp Glu Leu Gln Ala Thr Glu Asp Ala Lys Leu Arg Leu Glu Val Asn
        1555                1560                1565
Met Gln Ala Leu Lys Gly Gln Phe Glu Arg Asp Leu Gln Ala Arg Asp
    1570                1575                1580
Glu Gln Asn Glu Glu Lys Arg Arg Gln Leu Gln Arg Gln Leu His Glu
1585                1590                1595                1600
Tyr Glu Thr Glu Leu Glu Asp Glu Arg Lys Gln Arg Ala Leu Ala Ala
                1605                1610                1615
Ala Ala Lys Lys Lys Leu Glu Gly Asp Leu Lys Asp Leu Glu Leu Gln
            1620                1625                1630
```

Ala Asp Ser Ala Ile Lys Gly Arg Glu Glu Ala Ile Lys Gln Leu Arg
1635 1640 1645
Lys Leu Gln Ala Gln Met Lys Asp Phe Gln Arg Glu Leu Glu Asp Ala
1650 1655 1660
Arg Ala Ser Arg Asp Glu Ile Phe Ala Thr Ala Lys Glu Asn Glu Lys
1665 1670 1675 1680
Lys Ala Lys Ser Leu Glu Ala Asp Leu Met Gln Leu Gln Glu Asp Leu
1685 1690 1695
Ala Ala Ala Glu Arg Ala Arg Lys Gln Ala Asp Leu Glu Lys Glu Glu
1700 1705 1710
Leu Ala Glu Glu Leu Ala Ser Ser Leu Ser Gly Arg Asn Ala Leu Gln
1715 1720 1725
Asp Glu Lys Arg Arg Leu Glu Ala Arg Ile Ala Gln Leu Glu Glu Glu
1730 1735 1740
Leu Glu Glu Glu Gln Gly Asn Met Glu Ala Met Ser Asp Arg Val Arg
1745 1750 1755 1760
Lys Ala Thr Gln Gln Ala Glu Gln Leu Ser Asn Glu Leu Ala Thr Glu
1765 1770 1775
Arg Ser Thr Ala Gln Lys Asn Glu Ser Ala Arg Gln Gln Leu Glu Arg
1780 1785 1790
Gln Asn Lys Glu Leu Arg Ser Lys Leu His Glu Met Glu Gly Ala Val
1795 1800 1805
Lys Ser Lys Phe Lys Ser Thr Ile Ala Ala Leu Glu Ala Lys Ile Ala
1810 1815 1820
Gln Leu Glu Glu Gln Val Glu Gln Glu Ala Arg Glu Lys Gln Ala Ala
1825 1830 1835 1840
Thr Lys Ser Leu Lys Gln Lys Asp Lys Lys Leu Lys Glu Ile Leu Leu
1845 1850 1855
Gln Val Glu Asp Glu Arg Lys Met Ala Glu Gln Tyr Lys Glu Gln Ala
1860 1865 1870
Glu Lys Gly Asn Ala Arg Val Lys Gln Leu Lys Arg Gln Leu Glu Glu
1875 1880 1885
Ala Glu Glu Glu Ser Gln Arg Ile Asn Ala Asn Arg Arg Lys Leu Gln
1890 1895 1900
Arg Glu Leu Asp Glu Ala Thr Glu Ser Asn Glu Ala Met Gly Arg Glu
1905 1910 1915 1920
Val Asn Ala Leu Lys Ser Lys Leu Arg Gly Pro Pro Pro Gln Glu Thr
1925 1930 1935
Ser Gln

<210> 165
<211> 958
<212> DNA
<213> Homo sapiens

<400> 165
tctaaagctc agtggagctg ggtcatctca ggccttggct ccttgaactt ttggccgcca 60
tgtgcttccc gaaggtcctc tctgatgaca tgaagaagct gaaggcccga atggtaatgc 120
tcctccctac ttctgctcag gggttggggg cctgggtctc agcgtgtgac actgaggaca 180
ctgtgggaca cctgggaccc tggagggaca aggatccggc cctttggtgc caactctgcc 240
tctcttcaca gcaccaggcc atagaaagat tttatgataa aatgcaaaat gcagaatcag 300
gacgtggaca ggtgatgtcg agcctggcag agctggagga cgacttcaaa gagggctacc 360
tggagacagt ggcggcttat tatgaggagc agcacccaga gctcactcct ctacttgaaa 420
aagaaagaga tggattacgg tgccgaggca acagatcccc tgtcccggat gttgaggatc 480
ccgcaaccga ggagcctggg gagagctttt gtracaaggt catgagatgg ttccaggcca 540
tgctgcagcg gctgcagacc tggtggcacg gggttctggc ctgggtgaag gagaaggtgg 600
tggccctggt ccatgcagtg caggccctct ggaaacagtt ccagagtttc tgctgctctc 660

```
tgtcagagct cttcatgtcc tctttccagt cctacggagc cccacggggg gacaaggagg 720
agctgacacc ccagaagtgc tctgaacccc aatcctcaaa atgaagatac tgacaccacc 780
tttgccctcc ccgtcaccgc gcacccaccc tgacccctcc ctcagctgtc ctgtgccccg 840
ccctctcccg cacactcagt ccccctgcct ggcgttcctg ccgcagctct gacctggtgc 900
tgtcgccctg gcatcttaat aaaacctgct tatacttccc tggcagggag ataccatg   958
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<210> 166
<211> 234
<212> PRT
<213> Homo sapiens

<400> 166

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Met Cys Phe Pro Lys Val Leu Ser Asp Asp Met Lys Lys Leu Lys Ala
 1               5                  10                  15
Arg Met Val Met Leu Leu Pro Thr Ser Ala Gln Gly Leu Gly Ala Trp
            20                  25                  30
Val Ser Ala Cys Asp Thr Glu Asp Thr Val Gly His Leu Gly Pro Trp
        35                  40                  45
Arg Asp Lys Asp Pro Ala Leu Trp Cys Gln Leu Cys Leu Ser Ser Gln
    50                  55                  60
His Gln Ala Ile Glu Arg Phe Tyr Asp Lys Met Gln Asn Ala Glu Ser
65                  70                  75                  80
Gly Arg Gly Gln Val Met Ser Ser Leu Ala Glu Leu Glu Asp Asp Phe
                85                  90                  95
Lys Glu Gly Tyr Leu Glu Thr Val Ala Ala Tyr Tyr Glu Glu Gln His
            100                 105                 110
Pro Glu Leu Thr Pro Leu Leu Glu Lys Glu Arg Asp Gly Leu Arg Cys
        115                 120                 125
Arg Gly Asn Arg Ser Pro Val Pro Asp Val Glu Asp Pro Ala Thr Glu
    130                 135                 140
Glu Pro Gly Glu Ser Phe Cys Asx Lys Val Met Arg Trp Phe Gln Ala
145                 150                 155                 160
Met Leu Gln Arg Leu Gln Thr Trp Trp His Gly Val Leu Ala Trp Val
                165                 170                 175
Lys Glu Lys Val Val Ala Leu Val His Ala Val Gln Ala Leu Trp Lys
            180                 185                 190
Gln Phe Gln Ser Phe Cys Cys Ser Leu Ser Glu Leu Phe Met Ser Ser
        195                 200                 205
Phe Gln Ser Tyr Gly Ala Pro Arg Gly Asp Lys Glu Glu Leu Thr Pro
    210                 215                 220
Gln Lys Cys Ser Glu Pro Gln Ser Ser Lys
225                 230
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<210> 167
<211> 958
<212> DNA
<213> Homo sapiens

<400> 167

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tctaaagctc agtggagctg ggtcatctca ggccttggct ccttgaactt ttggccgcca 60
tgtgcttccc gaaggtcctc tctgatgaca tgaagaagct gaaggcccga atggtaatgc 120
tcctccctac ttctgctcag ggggttgggg cctgggtctc agcgtgtgac actgaggaca 180
ctgtgggaca cctgggaccc tggagggaca aggatccggc cctttggtgc caactctgcc 240
tctcttcaca gcaccaggcc atagaaagat tttatgataa aatgcaaaat gcagaatcag 300
gacgtggaca ggtgatgtcg agcctggcag agctggagga cgacttcaaa gagggctacc 360
tggagacagt ggcggcttat tatgaggagc agcacccaga gctcactcct ctacttgaaa 420
aagaaagaga tggattacgg tgccgaggca acagatcccc tgtcccggat gttgaggatc 480
ccgcaaccga ggagcctggg gagagctttt gtgacaaggt catgagatgg ttccaggcca 540
```

```
tgctgcagcg gctgcagacc tggtggcacg gggttctggc ctgggtgaag gagaaggtgg 600
tggccctggt ccatgcagtg caggccctct ggaaacagtt ccagagtttc tgctgctctc 660
tgtcagagct cttcatgtcc tctttccagt cctacggagc cccacggggg gacaaggagg 720
agctgacacc ccagaagtgc tctgaacccc aatcctcaaa atgaagatac tgacaccacc 780
tttgccctcc ccgtcaccgc gcacccaccc tgacccctcc ctcagctgtc ctgtgccccg 840
ccctctcccg cacactcagt ccccctgcct ggcgttcctg ccgcagctct gacctggtgc 900
tgtcgccctg gcatcttaat aaaacctgct tatacttccc tggcagggag ataccatg   958
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<210> 168
<211> 234
<212> PRT
<213> Homo sapiens

<400> 168

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Met Cys Phe Pro Lys Val Leu Ser Asp Asp Met Lys Lys Leu Lys Ala
1               5                   10                  15
Arg Met Val Met Leu Leu Pro Thr Ser Ala Gln Gly Leu Gly Ala Trp
            20                  25                  30
Val Ser Ala Cys Asp Thr Glu Asp Thr Val Gly His Leu Gly Pro Trp
        35                  40                  45
Arg Asp Lys Asp Pro Ala Leu Trp Cys Gln Leu Cys Leu Ser Ser Gln
    50                  55                  60
His Gln Ala Ile Glu Arg Phe Tyr Asp Lys Met Gln Asn Ala Glu Ser
65                  70                  75                  80
Gly Arg Gly Gln Val Met Ser Ser Leu Ala Glu Leu Glu Asp Asp Phe
                85                  90                  95
Lys Glu Gly Tyr Leu Glu Thr Val Ala Ala Tyr Tyr Glu Glu Gln His
            100                 105                 110
Pro Glu Leu Thr Pro Leu Leu Glu Lys Glu Arg Asp Gly Leu Arg Cys
        115                 120                 125
Arg Gly Asn Arg Ser Pro Val Pro Asp Val Glu Asp Pro Ala Thr Glu
    130                 135                 140
Glu Pro Gly Glu Ser Phe Cys Asp Lys Val Met Arg Trp Phe Gln Ala
145                 150                 155                 160
Met Leu Gln Arg Leu Gln Thr Trp Trp His Gly Val Leu Ala Trp Val
                165                 170                 175
Lys Glu Lys Val Val Ala Leu Val His Ala Val Gln Ala Leu Trp Lys
            180                 185                 190
Gln Phe Gln Ser Phe Cys Cys Ser Leu Ser Glu Leu Phe Met Ser Ser
        195                 200                 205
Phe Gln Ser Tyr Gly Ala Pro Arg Gly Asp Lys Glu Glu Leu Thr Pro
    210                 215                 220
Gln Lys Cys Ser Glu Pro Gln Ser Ser Lys
225                 230
```

<210> 169
<211> 1005
<212> DNA
<213> Homo sapiens

<400> 169

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tgtgctgcta ttgtgtggat gccgcgcgtg tcttctcttc tttccagaga tggctaacag 60
gggcccgagc tatggcttaa gccgagaggt gcaggagaag atcgagcaga agtatgatgc 120
ggacctggag aacaagctgg tggactggat catcctgcag tgcgccgagg acatagagca 180
cccgcccccc ggcagggccc attttcagaa atggttaatg gacgggacgg tcctgtgcaa 240
gctgataaat agtttatacc caccaggaca agagcccata cccaagatct cagagtcaaa 300
gatggctttt aagcagatgg agcaaatctc ccagttccta aaagctgcgg agacctatgg 360
tgtcagaacc accgacatct ttcagacggt ggatctatgg gaagggaagg acatggcagc 420
```

```
tgtgcagagg accctgatgg ctttaggcag cgttgcagtc accaaggatg atggctgcta 480
tcggggagag ccatcctggt ttcacaggaa agcccagcag aatcggagag gcttttccga 540
ggagcagctt cgccagggac agaacgtaat aggcctgcag atgggcagca acaagggagc 600
ctcccaggcg ggcatgacag ggtacgggat gcccaggcag atcatgttag gacgcggcat 660
cctgcccctg gtagagagga cgaatgttcc acaccatggt ctctacgaaa aagaaatagt 720
tagtcacctt ctgaccttct cctctttctc aaagccttct gtccctggtt tttgcaagtg 780
ctgcatttcc gccgagaatc cgcgttgcct actgctgcca cctcctgttc atttagaact 840
atgcaaagac tccgcttccg ttttcctgag ctcctcgggc cccagagtct ctgtttgatt 900
atttatttat ttatttattt atttgccaaa aattctcctc ttcaacttat agaatgcacc 960
taataaagta attaagtctt gtggaaaaaa aaaaaaaaaa aaaaa                1005
```

<210> 170
<211> 282
<212> PRT
<213> Homo sapiens

<400> 170

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Met Ala Asn Arg Gly Pro Ser Tyr Gly Leu Ser Arg Glu Val Gln Glu
 1               5                  10                  15
Lys Ile Glu Gln Lys Tyr Asp Ala Asp Leu Glu Asn Lys Leu Val Asp
            20                  25                  30
Trp Ile Ile Leu Gln Cys Ala Glu Asp Ile Glu His Pro Pro Pro Gly
        35                  40                  45
Arg Ala His Phe Gln Lys Trp Leu Met Asp Gly Thr Val Leu Cys Lys
    50                  55                  60
Leu Ile Asn Ser Leu Tyr Pro Pro Gly Gln Glu Pro Ile Pro Lys Ile
65                  70                  75                  80
Ser Glu Ser Lys Met Ala Phe Lys Gln Met Glu Gln Ile Ser Gln Phe
                85                  90                  95
Leu Lys Ala Ala Glu Thr Tyr Gly Val Arg Thr Thr Asp Ile Phe Gln
            100                 105                 110
Thr Val Asp Leu Trp Glu Gly Lys Asp Met Ala Ala Val Gln Arg Thr
        115                 120                 125
Leu Met Ala Leu Gly Ser Val Ala Val Thr Lys Asp Asp Gly Cys Tyr
    130                 135                 140
Arg Gly Glu Pro Ser Trp Phe His Arg Lys Ala Gln Gln Asn Arg Arg
145                 150                 155                 160
Gly Phe Ser Glu Glu Gln Leu Arg Gln Gly Gln Asn Val Ile Gly Leu
                165                 170                 175
Gln Met Gly Ser Asn Lys Gly Ala Ser Gln Ala Gly Met Thr Gly Tyr
            180                 185                 190
Gly Met Pro Arg Gln Ile Met Leu Gly Arg Gly Ile Leu Pro Leu Val
        195                 200                 205
Glu Arg Thr Asn Val Pro His His Gly Leu Tyr Glu Lys Glu Ile Val
    210                 215                 220
Ser His Leu Leu Thr Phe Ser Ser Phe Ser Lys Pro Ser Val Pro Gly
225                 230                 235                 240
Phe Cys Lys Cys Cys Ile Ser Ala Glu Asn Pro Arg Cys Leu Leu Leu
                245                 250                 255
Pro Pro Pro Val His Leu Glu Leu Cys Lys Asp Ser Ala Ser Val Phe
            260                 265                 270
Leu Ser Ser Ser Gly Pro Arg Val Ser Val
        275                 280
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<210> 171
<211> 942
<212> DNA
<213> Homo sapiens

<400> 171
atgagaattg cagtgatttg cttttgcctc ctaggcatca cctgtgccat accagttaaa 60
caggctgatt ctggaagttc tgaggaaaag cagctttaca acaaataccc agatgctgtg 120
gccacatggc taaaccctga cccatctcag aagcagaatc tcctagcccc acagaatgct 180
gtgtcctctg aagaaaccaa tgactttaaa caagagaccc ttccaagtaa gtccaacgaa 240
agccatgacc acatggatga tatggatgat gaagatgatg atgaccatgt ggacagccag 300
gactccattg actcgaacga ctctgatgat gtagatgaca ctgatgattc tcaccagtct 360
gatgagtctc accattctga tgaatctgat gaactggtca ctgatttttcc cacggacctg 420
ccagcaaccg aagttttcac tccagttgtc cccacagtag acacatatga tggccgaggt 480
gatagtgtgg tttatggact gaggtcaaaa tctaagaagt ttcgcagacc tgacatccag 540
taccctgatg ctacagacga gcacatcacc tcacacatgg aaagcgagga gttgaatggt 600
gcatacaagg ccatccccgt tgcccaggac ctgaacgcgc cttctgattg ggacagccgt 660
gggaaggaca gttatgaaac gagtcagctg gatgaccaga gtgctgaagc ccacagccac 720
aagcagtcca gattatataa gcggaaagct aatgatgaga gcaatgagca ttccgatgtg 780
attgatagtc aggaactttc caaagtcagc cgtgaattcc acagccatga atttcacagc 840
catgaagata tgctggttgt agaccccaaa agtaaggaag aagataaaca cctgaaattt 900
cgtatttctc atgaattaga tagtgcatct tctgaggtca at 942

<210> 172
<211> 314
<212> PRT
<213> Homo sapiens

<400> 172
Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
1 5 10 15
Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
20 25 30
Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
35 40 45
Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Asn Ala Val Ser Ser Glu
50 55 60
Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro Ser Lys Ser Asn Glu
65 70 75 80
Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp Asp His
85 90 95
Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp Val Asp
100 105 110
Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser Asp Glu
115 120 125
Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu
130 135 140
Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly Arg Gly
145 150 155 160
Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe Arg Arg
165 170 175
Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu His Ile Thr Ser His
180 185 190
Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro Val Ala
195 200 205
Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys Asp Ser
210 215 220
Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Ala His Ser His
225 230 235 240
Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser Asn Glu
245 250 255
His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser Arg Glu
260 265 270

```
Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val Val Asp
        275                 280                 285
Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile Ser His
    290                 295                 300
Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
305                 310


&lt;210&gt; 173
&lt;211&gt; 1524
&lt;212&gt; DNA
&lt;213&gt; Homo sapiens

&lt;400&gt; 173
gcagagcaca gcatcgtcgg gaccagactc gtctcaggcc agttgcagcc ttctcagcca 60
aacgccgacc aaggaaaact cactaccatg agaattgcag tgatttgctt ttgcctccta 120
ggcatcacct gtgccatacc agttaaacag gctgattctg gaagttctga ggaaaagcag 180
ctttacaaca aatacccaga tgctgtggcc acatggctaa accctgaccc atctcagaag 240
cagaatctcc tagccccaca gacccttcca agtaagtcca acgaaagcca tgaccacatg 300
gatgatatgg atgatgaaga tgatgatgac catgtggaca gccaggactc cattgactcg 360
aacgactctg atgatgtaga tgacactgat gattctcacc agtctgatga gtctcaccat 420
tctgatgaat ctgatgaact ggtcactgat tttcccacgg acctgccagc aaccgaagtt 480
ttcactccag ttgtccccac agtagacaca tatgatggcc gaggtgatag tgtggtttat 540
ggactgaggt caaaatctaa gaagtttcgc agacctgaca tccagtaccc tgatgctaca 600
gacgaggaca tcacctcaca catggaaagc gaggagttga atggtgcata caaggccatc 660
cccgttgccc aggacctgaa cgcgccttct gattgggaca gccgtgggaa ggacagttat 720
gaaacgagtc agctggatga ccagagtgct gaaacccaca gccacaagca gtccagatta 780
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gcctaaaaaa aaaaaaaaaa aaaa                                        1524

&lt;210&gt; 174
&lt;211&gt; 300
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 174
Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
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Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
            20                  25                  30
Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
        35                  40                  45
Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Thr Leu Pro Ser Lys Ser
    50                  55                  60
Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp
65                  70                  75                  80
Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp
                85                  90                  95
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Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser
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Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala
115 120 125
Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly
130 135 140
Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe
145 150 155 160
Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr
165 170 175
Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro
180 185 190
Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys
195 200 205
Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His
210 215 220
Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser
225 230 235 240
Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser
245 250 255
Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val
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Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile
275 280 285
Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
290 295 300

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<211> 861
<212> DNA
<213> Homo sapiens

<400> 175
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gactttaaac aagagaccct tccaagtaag tccaacgaaa gccatgacca catggatgat 180
atggatgatg aagatgatga tgaccatgtg gacagccagg actccattga ctcgaacgac 240
tctgatgatg tagatgacac tgatgattct caccagtctg atgagtctca ccattctgat 300
gaatctgatg aactggtcac tgattttccc acggacctgc cagcaaccga agttttcact 360
ccagttgtcc ccacagtaga cacatatgat ggccgaggtg atagtgtggt ttatggactg 420
aggtcaaaat ctaagaagtt tcgcagacct gacatccagt accctgatgc tacagacgag 480
cacatcacct cacacatgga aagcgaggag ttgaatggtg catacaaggc catccccgtt 540
gcccaggacc tgaacgcgcc ttctgattgg gacagccgtg ggaaggacag ttatgaaacg 600
agtcagctgg atgaccagag tgctgaagcc cacagccaca agcagtccag attatataag 660
cggaaagcta atgatgagag caatgagcat tccgatgtga ttgatagtca ggaactttcc 720
aaagtcagcc gtgaattcca cagccatgaa tttcacagcc atgaagatat gctggttgta 780
gaccccaaaa gtaaggaaga agataaacac ctgaaatttc gtatttctca tgaattagat 840
agtgcatctt ctgaggtcaa t 861

<210> 176
<211> 287
<212> PRT
<213> Homo sapiens

<400> 176
Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
1 5 10 15
Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Asn

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Ala Val Ser Ser Glu Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro
        35                  40                  45
Ser Lys Ser Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu
    50                  55                  60
Asp Asp Asp Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp
65                  70                  75                  80
Ser Asp Asp Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser
                85                  90                  95
His His Ser Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp
            100                 105                 110
Leu Pro Ala Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr
        115                 120                 125
Tyr Asp Gly Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser
    130                 135                 140
Lys Lys Phe Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu
145                 150                 155                 160
His Ile Thr Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys
                165                 170                 175
Ala Ile Pro Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser
            180                 185                 190
Arg Gly Lys Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala
        195                 200                 205
Glu Ala His Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn
    210                 215                 220
Asp Glu Ser Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser
225                 230                 235                 240
Lys Val Ser Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp
                245                 250                 255
Met Leu Val Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys
            260                 265                 270
Phe Arg Ile Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
        275                 280                 285
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<210> 177
<211> 3213
<212> DNA
<213> Homo sapiens

<400> 177

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gggaccaagg cccaaatgtc tgtgcccttc aacagatttt gggcaccaaa aagaaatact 180
tcagcacttg taagaactgg tataaaaagt ccatctgtgg acagaaaacg actgttttat 240
atgaatgttg ccctggttat atgagaatgg aaggaatgaa aggctgccca gcagttttgc 300
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tgaatgttga attactgaat gctttacata gtcacatgat taataagaga atgttgacca 540
aggacttaaa aaatggcatg attattcctt caatgtataa caatttgggg cttttcatta 600
accattatcc taatggggtt gtcactgtta attgtgctcg aatcatccat gggaaccaga 660
ttgcaacaaa tggtgttgtc catgtcattg accgtgtgct tacacaaatt ggtacctcaa 720
ttcaagactt cattgaagca gaagatgacc tttcatcttt tagagcagct gccatcacat 780
cggacatatt ggaggccctt ggaagagacg gtcacttcac actctttgct cccaccaatg 840
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gtataacagt aaatggaatc aaaatggtga acaaaaagga tattgtgaca aataatggtg 1080
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<210> 178
<211> 836
<212> PRT
<213> Homo sapiens

<400> 178
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Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln
35 40 45
Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr
50 55 60
Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
65 70 75 80
Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu
85 90 95
Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
100 105 110
Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly
115 120 125

Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala Trp Asp Asn
130 135 140
Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val Asn Val Glu
145 150 155 160
Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg Met Leu Thr
165 170 175
Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr Asn Asn Leu
180 185 190
Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr Val Asn Cys
195 200 205
Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly Val Val His
210 215 220
Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile Gln Asp Phe
225 230 235 240
Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala Ala Ile Thr
245 250 255
Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe Thr Leu Phe
260 265 270
Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly Val Leu Glu
275 280 285
Arg Phe Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met Lys Tyr His
290 295 300
Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly Gly Ala Val
305 310 315 320
Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys Asp Gly Asp
325 330 335
Ser Ile Thr Val Asn Gly Ile Lys Met Val Asn Lys Lys Asp Ile Val
340 345 350
Thr Asn Asn Gly Val Ile His Leu Ile Asp Gln Val Leu Ile Pro Asp
355 360 365
Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln Thr Thr Phe
370 375 380
Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu Arg Pro Asp
385 390 395 400
Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe Ser Asp Asp
405 410 415
Thr Leu Ser Met Val Gln Arg Leu Leu Lys Leu Ile Leu Gln Asn His
420 425 430
Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn Gly Gln Ile
435 440 445
Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val Tyr Arg Thr
450 455 460
Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser Lys Gln Gly
465 470 475 480
Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys Pro Ala Glu
485 490 495
Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe Ser Thr Phe
500 505 510
Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu Thr Gln Pro
515 520 525
Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe Lys Gly Met
530 535 540
Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn Ala Leu Gln
545 550 555 560
Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile Gly Lys Gly
565 570 575
Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln Gly Ser Lys
580 585 590
Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn Glu Leu Lys

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        595                 600                 605
Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile His Val Val
    610                 615                 620
Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn Asp Gln Leu
625                 630                 635                 640
Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val
                645                 650                 655
Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Thr Thr Lys
            660                 665                 670
Ile Ile Thr Lys Val Val Glu Pro Lys Ile Lys Val Ile Glu Gly Ser
        675                 680                 685
Leu Gln Pro Ile Ile Lys Thr Glu Gly Pro Thr Leu Thr Lys Val Lys
    690                 695                 700
Ile Glu Gly Glu Pro Glu Phe Arg Leu Ile Lys Glu Gly Glu Thr Ile
705                 710                 715                 720
Thr Glu Val Ile His Gly Glu Pro Ile Ile Lys Lys Tyr Thr Lys Ile
                725                 730                 735
Ile Asp Gly Val Pro Val Glu Ile Thr Glu Lys Glu Thr Arg Glu Glu
            740                 745                 750
Arg Ile Ile Thr Gly Pro Glu Ile Lys Tyr Thr Arg Ile Ser Thr Gly
        755                 760                 765
Gly Gly Glu Thr Glu Glu Thr Leu Lys Lys Leu Leu Gln Glu Glu Val
    770                 775                 780
Thr Lys Val Thr Lys Phe Ile Glu Gly Gly Asp Gly His Leu Phe Glu
785                 790                 795                 800
Asp Glu Glu Ile Lys Arg Leu Leu Gln Gly Asp Thr Pro Val Arg Lys
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Leu Gln Ala Asn Lys Lys Val Gln Gly Ser Arg Arg Arg Leu Arg Glu
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<210> 179
<211> 3077
<212> DNA
<213> Homo sapiens

<400> 179

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<210> 180
<211> 779
<212> PRT
<213> Homo sapiens

<400> 180
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20 25 30
Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln
35 40 45
Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr
50 55 60
Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
65 70 75 80
Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu
85 90 95
Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
100 105 110
Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly
115 120 125
Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala Trp Asp Asn
130 135 140
Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val Asn Val Glu
145 150 155 160

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Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg Met Leu Thr
                165                 170                 175
Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr Asn Asn Leu
            180                 185                 190
Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr Val Asn Cys
        195                 200                 205
Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly Val Val His
    210                 215                 220
Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile Gln Asp Phe
225                 230                 235                 240
Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala Ala Ile Thr
                245                 250                 255
Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe Thr Leu Phe
            260                 265                 270
Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly Val Leu Glu
        275                 280                 285
Arg Phe Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met Lys Tyr His
    290                 295                 300
Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly Gly Ala Val
305                 310                 315                 320
Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys Asp Gly Asp
                325                 330                 335
Ser Ile Thr Val Asn Gly Ile Lys Met Val Asn Lys Lys Asp Ile Val
            340                 345                 350
Thr Asn Asn Gly Val Ile His Leu Ile Asp Gln Val Leu Ile Pro Asp
        355                 360                 365
Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln Thr Thr Phe
    370                 375                 380
Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu Arg Pro Asp
385                 390                 395                 400
Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe Ser Asp Asp
                405                 410                 415
Thr Leu Ser Met Val Gln Arg Leu Leu Lys Leu Ile Leu Gln Asn His
            420                 425                 430
Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn Gly Gln Ile
        435                 440                 445
Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val Tyr Arg Thr
    450                 455                 460
Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser Lys Gln Gly
465                 470                 475                 480
Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys Pro Ala Glu
                485                 490                 495
Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe Ser Thr Phe
            500                 505                 510
Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu Thr Gln Pro
        515                 520                 525
Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe Lys Gly Met
    530                 535                 540
Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn Ala Leu Gln
545                 550                 555                 560
Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile Gly Lys Gly
                565                 570                 575
Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln Gly Ser Lys
            580                 585                 590
Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn Glu Leu Lys
        595                 600                 605
Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile His Val Val
    610                 615                 620
Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn Asp Gln Leu
```

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625                 630                 635                 640
Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val
                645                 650                 655
Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Lys Pro Ile
            660                 665                 670
Ile Lys Lys Tyr Thr Lys Ile Ile Asp Gly Val Pro Val Glu Ile Thr
        675                 680                 685
Glu Lys Glu Thr Arg Glu Glu Arg Ile Ile Thr Gly Pro Glu Ile Lys
    690                 695                 700
Tyr Thr Arg Ile Ser Thr Gly Gly Gly Glu Thr Glu Glu Thr Leu Lys
705                 710                 715                 720
Lys Leu Leu Gln Glu Glu Val Thr Lys Val Thr Lys Phe Ile Glu Gly
                725                 730                 735
Gly Asp Gly His Leu Phe Glu Asp Glu Glu Ile Lys Arg Leu Leu Gln
            740                 745                 750
Gly Asp Thr Pro Val Arg Lys Leu Gln Ala Asn Lys Lys Val Gln Gly
        755                 760                 765
Ser Arg Arg Arg Leu Arg Glu Gly Arg Ser Gln
    770                 775
```

```
<210> 181
<211> 2088
<212> DNA
<213> Homo sapiens

<400> 181
gaattcggca cgagcgcgcg gcgaatctca acgctgcgcc gtctgcgggc gcttccgggc 60
caccagtttc tctgctttcc accctggcgc cccccagccc tggctcccca gctgcgctgc 120
cccgggcgtc cacgccctgc gggcttagcg ggttcagtgg gctcaatctg cgcagcgcca 180
cctccatgtt gaccaagcct ctacaggggc ctcccgcgcc ccccgggacc cccacgccgc 240
cgccaggagg caaggatcgg gaagcgttcg aggccgagta tcgactcggc cccctcctgg 300
gtaagggggg ctttggcacc gtcttcgcag gacaccgcct cacagatcga ctccaggtgg 360
ccatcaaagt gattccccgg aatcgtgtgc tgggctggtc cccсttgtca gactcagtca 420
catgcccact cgaagtcgca ctgctatgga aagtgggtgc aggtggtggg caccctggcg 480
tgatccgcct gcttgactgg tttgagacac aggaaggctt catgctggtc ctcgagcggc 540
ctttgcccgc ccaggatctc tttgactata tcacagagaa gggcccactg ggtgaaggcc 600
caagccgctg cttctttggc caagtagtgg cagccatcca gcactgccat tcccgtggag 660
ttgtccatcg tgacatcaag gatgagaaca tcctgataga cctacgccgt ggctgtgcca 720
aactcattga ttttggttct ggtgccctgc ttcatgatga accctacact gactttgatg 780
ggacaagggt gtacagcccc ccagagtgga tctctcgaca ccagtaccat gcactcccgg 840
ccactgtctg gtcactgggc atcctcctct atgacatggt gtgtggggac attccctttg 900
agagggacca ggagattctg gaagctgagc tccacttccc agcccatgtc tccccagact 960
gctgtgccct aatccgccgg tgcctggccc ccaaaccttc ttcccgaccc tcactggaag 1020
agatcctgct ggacccctgg atgcaaacac cagccgagga tgttacccct caacccctcc 1080
aaaggaggcc ctgccccttt ggcctggtcc ttgctaccct aagcctggcc tggcctggcc 1140
tggcccccaa tggtcagaag agccatccca tggccatgtc acagggatag atggacattt 1200
gttgacttgg ttttacaggt cattaccagt cattaaagtc cagtattact aaggtaaggg 1260
attgaggatc aggggttaga agacataaac caagtttgcc cagttccctt cccaatccta 1320
caaaggagcc ttcctcccag aacctgtggt ccctgatttt ggagggggaa cttcttgctt 1380
ctcattttgc taaggaagtt tattttggtg aagttgttcc cattttgagc cccgggactc 1440
ttattttgat gatgtgtcac cccacattgg cacctcctac taccaccaca caaacttagt 1500
tcatatgctt ttacttgggc aagggtgctt tccttccaat accccagtag cttttatttt 1560
agtaaaggga ccctttcccc tagcctaggg tcccatattg ggtcaagctg cttacctgcc 1620
tcagcccagg atttttattt ttgggggagg taatgccctg ttgttacccc aaggcttctt 1680
tttttttttt tttttttttg ggtgagggga ccctactttg ttatcccaag tgctcttatt 1740
ctggtgagaa gaaccttaat tccataattt gggaaggaat ggaagatgga caccaccgga 1800
caccaccaga caataggatg ggatggatgg tttttggggg gatgggctag gggaaataag 1860
gcttgctgtt tgttttcctg ggcgctcccc tccaattttg cagatttttg caacctcctc 1920
```

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ctgagccggg attgtccaat tactaaaatg taaataatca cgtattgtgg ggaggggagt 1980
tccaagtgtg ccctcctttt ttttcctgcc tggattattt aaaaagccat gtgtggaaac 2040
ccactattta ataaaagtaa tagaatcaga aaaaaaaaaa aaaaaaaa              2088

<210> 182
<211> 334
<212> PRT
<213> Homo sapiens

<400> 182
Met Leu Thr Lys Pro Leu Gln Gly Pro Pro Ala Pro Pro Gly Thr Pro
 1               5                  10                  15
Thr Pro Pro Pro Gly Gly Lys Asp Arg Glu Ala Phe Glu Ala Glu Tyr
            20                  25                  30
Arg Leu Gly Pro Leu Leu Gly Lys Gly Gly Phe Gly Thr Val Phe Ala
        35                  40                  45
Gly His Arg Leu Thr Asp Arg Leu Gln Val Ala Ile Lys Val Ile Pro
    50                  55                  60
Arg Asn Arg Val Leu Gly Trp Ser Pro Leu Ser Asp Ser Val Thr Cys
65                  70                  75                  80
Pro Leu Glu Val Ala Leu Leu Trp Lys Val Gly Ala Gly Gly Gly His
                85                  90                  95
Pro Gly Val Ile Arg Leu Leu Asp Trp Phe Glu Thr Gln Glu Gly Phe
            100                 105                 110
Met Leu Val Leu Glu Arg Pro Leu Pro Ala Gln Asp Leu Phe Asp Tyr
        115                 120                 125
Ile Thr Glu Lys Gly Pro Leu Gly Glu Gly Pro Ser Arg Cys Phe Phe
    130                 135                 140
Gly Gln Val Val Ala Ala Ile Gln His Cys His Ser Arg Gly Val Val
145                 150                 155                 160
His Arg Asp Ile Lys Asp Glu Asn Ile Leu Ile Asp Leu Arg Arg Gly
                165                 170                 175
Cys Ala Lys Leu Ile Asp Phe Gly Ser Gly Ala Leu Leu His Asp Glu
            180                 185                 190
Pro Tyr Thr Asp Phe Asp Gly Thr Arg Val Tyr Ser Pro Pro Glu Trp
        195                 200                 205
Ile Ser Arg His Gln Tyr His Ala Leu Pro Ala Thr Val Trp Ser Leu
    210                 215                 220
Gly Ile Leu Leu Tyr Asp Met Val Cys Gly Asp Ile Pro Phe Glu Arg
225                 230                 235                 240
Asp Gln Glu Ile Leu Glu Ala Glu Leu His Phe Pro Ala His Val Ser
                245                 250                 255
Pro Asp Cys Cys Ala Leu Ile Arg Arg Cys Leu Ala Pro Lys Pro Ser
            260                 265                 270
Ser Arg Pro Ser Leu Glu Glu Ile Leu Leu Asp Pro Trp Met Gln Thr
        275                 280                 285
Pro Ala Glu Asp Val Thr Pro Gln Pro Leu Gln Arg Arg Pro Cys Pro
    290                 295                 300
Phe Gly Leu Val Leu Ala Thr Leu Ser Leu Ala Trp Pro Gly Leu Ala
305                 310                 315                 320
Pro Asn Gly Gln Lys Ser His Pro Met Ala Met Ser Gln Gly
                325                 330


<210> 183
<211> 2304
<212> DNA
<213> Homo sapiens
```

<400> 183
gtccccgcag cgccgtcgcg ccctcctgcc gcaggccacc gaggccgccg ccgtctagcg 60
ccccgacctc gccaccatga gagccctgct ggcgcgcctg cttctctgcg tcctggtcgt 120
gagcgactcc aaaggcagca atgaacttca tcaagttcca tcgaactgtg actgtctaaa 180
tggaggaaca tgtgtgtcca acaagtactt ctccaacatt cactggtgca actgcccaaa 240
gaaattcgga gggcagcact gtgaaataga taagtcaaaa acctgctatg aggggaatgg 300
tcacttttac cgaggaaagg ccagcactga caccatgggc cggccctgcc tgccctggaa 360
ctctgccact gtccttcagc aaacgtacca tgcccacaga tctgatgctc ttcagctggg 420
cctggggaaa cataattact gcaggaaccc agacaaccgg aggcgaccct ggtgctatgt 480
gcaggtgggc ctaaagccgc ttgtccaaga gtgcatggtg catgactgcg cagatggaaa 540
aaagccctcc tctcctccag aagaattaaa atttcagtgt ggccaaaaga ctctgaggcc 600
ccgctttaag attattgggg gagaattcac caccatcgag aaccagccct ggtttgcggc 660
catctacagg aggcaccggg ggggctctgt cacctacgtg tgtggaggca gcctcatcag 720
cccttgctgg gtgatcagcg ccacacactg cttcattgat tacccaaaga aggaggacta 780
catcgtctac ctgggtcgct caaggcttaa ctccaacacg caaggggaga tgaagtttga 840
ggtggaaaac ctcatcctac acaaggacta cagcgctgac acgcttgctc accacaacga 900
cattgccttg ctgaagatcc gttccaagga gggcaggtgt gcgcagccat cccggactat 960
acagaccatc tgcctgccct cgatgtataa cgatccccag tttggcacaa gctgtgagat 1020
cactggcttt ggaaaagaga attctaccga ctatctctat ccggagcagc tgaaaatgac 1080
tgttgtgaag ctgatttccc accgggagtg tcagcagccc cactactacg gctctgaagt 1140
caccaccaaa atgctatgtg ctgctgaccc ccaatggaaa acagattcct gccagggaga 1200
ctcaggggga cccctcgtct gttccctcca aggccgcatg actttgactg gaattgtgag 1260
ctggggccgt ggatgtgccc tgaaggacaa gccaggcgtc tacacgagag tctcacactt 1320
cttaccctgg atccgcagtc acaccaagga agagaatggc ctggccctct gagggtcccc 1380
agggaggaaa cgggcaccac ccgctttctt gctggttgtc atttttgcag tagagtcatc 1440
tccatcagct gtaagaagag actgggaaga taggctctgc acagatggat ttgcctgtgg 1500
caccaccagg gtgaacgaca atagctttac cctcacggat aggcctgggt gctggctgcc 1560
cagaccctct ggccaggatg gaggggtggt cctgactcaa catgttactg accagcaact 1620
tgtctttttc tggactgaag cctgcaggag ttaaaaaggg cagggcatct cctgtgcatg 1680
ggctcgaagg gagagccagc tcccccgacc ggtgggcatt tgtgaggccc atggttgaga 1740
aatgaataat ttcccaatta ggaagtgtaa gcagctgagg tctcttgagg gagcttagcc 1800
aatgtgggag cagcggtttg gggagcagag acactaacga cttcagggca gggctctgat 1860
attccatgaa tgtatcagga aatatatatg tgtgtgtatg tttgcacact tgttgtgtgg 1920
gctgtgagtg taagtgtgag taagagctgg tgtctgattg ttaagtctaa atatttcctt 1980
aaactgtgtg gactgtgatg ccacacagag tggtctttct ggagaggtta taggtcactc 2040
ctggggcctc ttgggtcccc cacgtgacag tgcctgggaa tgtacttatt ctgcagcatg 2100
acctgtgacc agcactgtct cagtttcact ttcacataga tgtccctttc ttggccagtt 2160
atcccttcct tttagcctag ttcatccaat cctcactggg tggggtgagg accactcctt 2220
acactgaata tttatatttc actattttta tttatatttt tgtaatttta aataaaagtg 2280
atcaataaaa tgtgattttt ctga 2304

<210> 184
<211> 431
<212> PRT
<213> Homo sapiens

<400> 184
Met Arg Ala Leu Leu Ala Arg Leu Leu Leu Cys Val Leu Val Val Ser
1 5 10 15
Asp Ser Lys Gly Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp
20 25 30
Cys Leu Asn Gly Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile
35 40 45
His Trp Cys Asn Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile
50 55 60
Asp Lys Ser Lys Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly
65 70 75 80
Lys Ala Ser Thr Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser
85 90 95

```
Ala Thr Val Leu Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu
            100                 105                 110
Gln Leu Gly Leu Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg
        115                 120                 125
Arg Arg Pro Trp Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln
    130                 135                 140
Glu Cys Met Val His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro
145                 150                 155                 160
Pro Glu Glu Leu Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg
                165                 170                 175
Phe Lys Ile Ile Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp
            180                 185                 190
Phe Ala Ala Ile Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val
        195                 200                 205
Cys Gly Gly Ser Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His
    210                 215                 220
Cys Phe Ile Asp Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly
225                 230                 235                 240
Arg Ser Arg Leu Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val
                245                 250                 255
Glu Asn Leu Ile Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His
            260                 265                 270
His Asn Asp Ile Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys
        275                 280                 285
Ala Gln Pro Ser Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr
    290                 295                 300
Asn Asp Pro Gln Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys
305                 310                 315                 320
Glu Asn Ser Thr Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val
                325                 330                 335
Val Lys Leu Ile Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly
            340                 345                 350
Ser Glu Val Thr Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys
        355                 360                 365
Thr Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu
    370                 375                 380
Gln Gly Arg Met Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys
385                 390                 395                 400
Ala Leu Lys Asp Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu
                405                 410                 415
Pro Trp Ile Arg Ser His Thr Lys Glu Glu Asn Gly Leu Ala Leu
            420                 425                 430
```

<210> 185
<211> 2123
<212> DNA
<213> Homo sapiens

<400> 185

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gggaggagcg gagcggtgcg gaggctctgc tcggatcgag gtctgcagcg cagcttcggg 60
agcatgagtg ctgcagtgac tgcagggaag ctggcacggg caccggccga ccctgggaaa 120
gccggggtcc ccggagttgc agctcccgga gctccggcgg cggctccacc ggcgaaagag 180
atcccggagg tcctagtgga cccacgcagc cggcggcgct atgtgcgggg ccgcttttg 240
ggcaagggcg gctttgccaa gtgcttcgag atctcggacg cggacaccaa ggaggtgttc 300
gcgggcaaga ttgtgcctaa gtctctgctg ctcaagccgc accagaggga gaagatgtcc 360
atggaaatat ccattcaccg cagcctcgcc caccagcacg tcgtaggatt ccacggcttt 420
ttcgaggaca acgacttcgt gttcgtggtg ttggagctct gccgccggag gtctctcctg 480
gagccgcaca agaggaggaa agccctgact gagcctgagg cccgatacta cctacggcaa 540
```

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attgtgcttg gctgccagta cctgcaccga aaccgagtta ttcatcgaga cctcaagctg 600
ggcaaccttt tcctgaatga agatctggag gtgaaaatag gggattttgg actggcaacc 660
aaagtcgaat atgacgggga gaggaagaag accctgtgtg ggactcctaa ttacatagct 720
cccgaggtgc tgagcaagaa agagcacagt ttcgaggtgg atgtgtggtc cattgggtgt 780
atcatgtata ccttgttagt gggcaaacca ccttttgaga cttcttgcct aaaagagacc 840
tacctccgga tcaagaagaa tgaatacagt attcccaagc acatcaaccc cgtggccgcc 900
tccctcatcc agaagatgct tcagacagat cccactgccc gcccaaccat taacgagctg 960
cttaatgacg agttctttac ttctggctat atccctgccc gtctccccat cacctgcctg 1020
accattccac caaggttttc gattgctccc agcagcctgg accccagcaa ccggaagccc 1080
ctcacagtcc tcaataaagg cttggagaac cccctgcctg agcgtccccg ggaaaaagaa 1140
gaaccagtgg ttcgagagac aggtgaggtg gtcgactgcc acctcagtga catgctgcag 1200
cagctgcaca gtgtcaatgc ctccaagccc tcggagcgtg ggctggtcag gcaagaggag 1260
gctgaggatc ctgcctgcat ccccatcttc tgggtcagca agtgggtgga ctattcggac 1320
aagtacggcc ttgggtatca gctctgtgat aacagcgtgg gggtgctctt caatgactca 1380
acacgcctca tcctctacaa tgatggtgac agcctgcagt acatagagcg tgacggcact 1440
gagtcctacc tcaccgtgag ttcccatccc aactccttga tgaagaagat caccctcctt 1500
aaatatttcc gcaattacat gagcgagcac ttgctgaagg caggtgccaa catcacgccg 1560
cgcgaaggtg atgagctcgc ccggctgccc tacctacgga cctggttccg cacccgcagc 1620
gccatcatcc tgcacctcag caacggcagc gtgcagatca acttcttcca ggatcacacc 1680
aagctcatct tgtgcccact gatggcagcc gtgacctaca tcgacgagaa gcgggacttc 1740
cgcacatacc gcctgagtct cctggaggag tacggctgct gcaaggagct ggccagccgg 1800
ctccgctacg cccgcactat ggtggacaag ctgctgagct cacgctcggc cagcaaccgt 1860
ctcaaggcct cctaatagct gccctcccct ccggactggt gccctcctca ctcccacctg 1920
catctggggc ccatactggt tggctcccgc ggtgccatgt ctgcagtgtg ccccccagcc 1980
ccggtggctg ggcagagctg catcatcctt gcaggtgggg gttgctgtat aagttatttt 2040
tgtacatgtt cgggtgtggg ttctacagac ttgtccccct ccccctcaac cccaccatat 2100
gaattgtaca gaatatttct att                                         2123
```

<210> 186
<211> 603
<212> PRT
<213> Homo sapiens

<400> 186

```
Met Ser Ala Ala Val Thr Ala Gly Lys Leu Ala Arg Ala Pro Ala Asp
 1               5                  10                  15
Pro Gly Lys Ala Gly Val Pro Gly Val Ala Ala Pro Gly Ala Pro Ala
            20                  25                  30
Ala Ala Pro Pro Ala Lys Glu Ile Pro Glu Val Leu Val Asp Pro Arg
        35                  40                  45
Ser Arg Arg Arg Tyr Val Arg Gly Arg Phe Leu Gly Lys Gly Gly Phe
    50                  55                  60
Ala Lys Cys Phe Glu Ile Ser Asp Ala Asp Thr Lys Glu Val Phe Ala
65                  70                  75                  80
Gly Lys Ile Val Pro Lys Ser Leu Leu Leu Lys Pro His Gln Arg Glu
                85                  90                  95
Lys Met Ser Met Glu Ile Ser Ile His Arg Ser Leu Ala His Gln His
            100                 105                 110
Val Val Gly Phe His Gly Phe Phe Glu Asp Asn Asp Phe Val Phe Val
        115                 120                 125
Val Leu Glu Leu Cys Arg Arg Arg Ser Leu Leu Glu Pro His Lys Arg
    130                 135                 140
Arg Lys Ala Leu Thr Glu Pro Glu Ala Arg Tyr Tyr Leu Arg Gln Ile
145                 150                 155                 160
Val Leu Gly Cys Gln Tyr Leu His Arg Asn Arg Val Ile His Arg Asp
                165                 170                 175
Leu Lys Leu Gly Asn Leu Phe Leu Asn Glu Asp Leu Glu Val Lys Ile
            180                 185                 190
Gly Asp Phe Gly Leu Ala Thr Lys Val Glu Tyr Asp Gly Glu Arg Lys
```

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        195                 200                 205
Lys Thr Leu Cys Gly Thr Pro Asn Tyr Ile Ala Pro Glu Val Leu Ser
    210                 215                 220
Lys Lys Glu His Ser Phe Glu Val Asp Val Trp Ser Ile Gly Cys Ile
225                 230                 235                 240
Met Tyr Thr Leu Leu Val Gly Lys Pro Pro Phe Glu Thr Ser Cys Leu
                245                 250                 255
Lys Glu Thr Tyr Leu Arg Ile Lys Lys Asn Glu Tyr Ser Ile Pro Lys
            260                 265                 270
His Ile Asn Pro Val Ala Ala Ser Leu Ile Gln Lys Met Leu Gln Thr
        275                 280                 285
Asp Pro Thr Ala Arg Pro Thr Ile Asn Glu Leu Leu Asn Asp Glu Phe
    290                 295                 300
Phe Thr Ser Gly Tyr Ile Pro Ala Arg Leu Pro Ile Thr Cys Leu Thr
305                 310                 315                 320
Ile Pro Pro Arg Phe Ser Ile Ala Pro Ser Ser Leu Asp Pro Ser Asn
                325                 330                 335
Arg Lys Pro Leu Thr Val Leu Asn Lys Gly Leu Glu Asn Pro Leu Pro
            340                 345                 350
Glu Arg Pro Arg Glu Lys Glu Glu Pro Val Val Arg Glu Thr Gly Glu
        355                 360                 365
Val Val Asp Cys His Leu Ser Asp Met Leu Gln Gln Leu His Ser Val
    370                 375                 380
Asn Ala Ser Lys Pro Ser Glu Arg Gly Leu Val Arg Gln Glu Glu Ala
385                 390                 395                 400
Glu Asp Pro Ala Cys Ile Pro Ile Phe Trp Val Ser Lys Trp Val Asp
                405                 410                 415
Tyr Ser Asp Lys Tyr Gly Leu Gly Tyr Gln Leu Cys Asp Asn Ser Val
            420                 425                 430
Gly Val Leu Phe Asn Asp Ser Thr Arg Leu Ile Leu Tyr Asn Asp Gly
        435                 440                 445
Asp Ser Leu Gln Tyr Ile Glu Arg Asp Gly Thr Glu Ser Tyr Leu Thr
    450                 455                 460
Val Ser Ser His Pro Asn Ser Leu Met Lys Lys Ile Thr Leu Leu Lys
465                 470                 475                 480
Tyr Phe Arg Asn Tyr Met Ser Glu His Leu Leu Lys Ala Gly Ala Asn
                485                 490                 495
Ile Thr Pro Arg Glu Gly Asp Glu Leu Ala Arg Leu Pro Tyr Leu Arg
            500                 505                 510
Thr Trp Phe Arg Thr Arg Ser Ala Ile Ile Leu His Leu Ser Asn Gly
        515                 520                 525
Ser Val Gln Ile Asn Phe Phe Gln Asp His Thr Lys Leu Ile Leu Cys
    530                 535                 540
Pro Leu Met Ala Ala Val Thr Tyr Ile Asp Glu Lys Arg Asp Phe Arg
545                 550                 555                 560
Thr Tyr Arg Leu Ser Leu Leu Glu Glu Tyr Gly Cys Cys Lys Glu Leu
                565                 570                 575
Ala Ser Arg Leu Arg Tyr Ala Arg Thr Met Val Asp Lys Leu Leu Ser
            580                 585                 590
Ser Arg Ser Ala Ser Asn Arg Leu Lys Ala Ser
        595                 600
```

<210> 187
<211> 2617
<212> DNA
<213> Homo sapiens

<400> 187

aagcagtctc aagcctgccg cagggagaag atggcggtcg ccgtgagaac tttgcaggaa 60
cagctggaaa aggccaaaga gagtcttaag aacgtggatg agaacattcg caagctcacc 120
gggcgggacc cgaatgatgt gaggcccatc caagccagat tgctggccct ttctggtcct 180
ggtggaggta gaggacgtgg tagtttattg ctgaggcgtg gattctcaga tagtggagga 240
cccccagcca aacagagaga ccttgaaggg gcagtcagta ggctgggcgg ggagcgtcgg 300
accagaagag aatcacgcca ggaaagcgac ccggaggatg atgatgttaa aaagccagca 360
ttgcagtctt cagttgtagc tacctccaaa gagcgcacac gtagagacct tatccaggat 420
caaaatatgg atgaaaaggg aaagcaaagg aaccgacgaa tatttggctt attgatgggc 480
actcttcaga aatttaaaca agaatccact gttgctactg aaaggcaaaa caggcgccag 540
gaaattgaac aaaaacttga agtgcaggcg gaagaagaaa gaaagcaggt tgaaaatgaa 600
aggagagaac tgtttgaaga gaggcgtgct aaacagacag aactgcggct tttagaacag 660
aaggttgagc ttgcgcagct gcaagaagaa tggaatgaac ataatgccaa aataattaaa 720
tatataagaa ctaagacaaa gccccatttg ttttatattc ccggaagaat gtgtccagct 780
acccaaaaac taatagaaga gtcacagaga aaaatgaacg ctttatttga tggtagacgc 840
atcgaatttg cagaacaaat aaataaaatg gaggctaggc ctagaagaca atcaatgaag 900
gaaaaagagc atcaggtggt gcgtaatgaa gaacacaagg cggaacaaga agagggtaag 960
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<210> 188
<211> 743
<212> PRT
<213> Homo sapiens

<400> 188
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Glu Ser Leu Lys Asn Val Asp Glu Asn Ile Arg Lys Leu Thr Gly Arg
            20   25   30
Asp Pro Asn Asp Val Arg Pro Ile Gln Ala Arg Leu Leu Ala Leu Ser
        35   40   45
Gly Pro Gly Gly Gly Arg Gly Arg Gly Ser Leu Leu Leu Arg Arg Gly
    50   55   60

Phe Ser Asp Ser Gly Gly Pro Pro Ala Lys Gln Arg Asp Leu Glu Gly
65 70 75 80
Ala Val Ser Arg Leu Gly Gly Glu Arg Arg Thr Arg Arg Glu Ser Arg
85 90 95
Gln Glu Ser Asp Pro Glu Asp Asp Asp Val Lys Lys Pro Ala Leu Gln
100 105 110
Ser Ser Val Val Ala Thr Ser Lys Glu Arg Thr Arg Arg Asp Leu Ile
115 120 125
Gln Asp Gln Asn Met Asp Glu Lys Gly Lys Gln Arg Asn Arg Arg Ile
130 135 140
Phe Gly Leu Leu Met Gly Thr Leu Gln Lys Phe Lys Gln Glu Ser Thr
145 150 155 160
Val Ala Thr Glu Arg Gln Asn Arg Arg Gln Glu Ile Glu Gln Lys Leu
165 170 175
Glu Val Gln Ala Glu Glu Glu Arg Lys Gln Val Glu Asn Glu Arg Arg
180 185 190
Glu Leu Phe Glu Glu Arg Arg Ala Lys Gln Thr Glu Leu Arg Leu Leu
195 200 205
Glu Gln Lys Val Glu Leu Ala Gln Leu Gln Glu Glu Trp Asn Glu His
210 215 220
Asn Ala Lys Ile Ile Lys Tyr Ile Arg Thr Lys Thr Lys Pro His Leu
225 230 235 240
Phe Tyr Ile Pro Gly Arg Met Cys Pro Ala Thr Gln Lys Leu Ile Glu
245 250 255
Glu Ser Gln Arg Lys Met Asn Ala Leu Phe Asp Gly Arg Arg Ile Glu
260 265 270
Phe Ala Glu Gln Ile Asn Lys Met Glu Ala Arg Pro Arg Arg Gln Ser
275 280 285
Met Lys Glu Lys Glu His Gln Val Val Arg Asn Glu Glu His Lys Ala
290 295 300
Glu Gln Glu Glu Gly Lys Val Ala Gln Arg Glu Glu Glu Leu Val Glu
305 310 315 320
Thr Gly Asn Gln His Asn Asp Val Glu Ile Glu Glu Ala Gly Glu Glu
325 330 335
Glu Glu Lys Glu Ile Gly Ile Val His Ser Asp Ala Glu Lys Glu Gln
340 345 350
Glu Glu Glu Glu Gln Lys Gln Glu Met Glu Val Lys Met Glu Glu Glu
355 360 365
Thr Glu Val Arg Glu Ser Glu Lys Gln Gln Asp Ser Gln Pro Glu Glu
370 375 380
Val Met Asp Val Leu Glu Met Val Glu Asn Val Lys His Val Ile Ala
385 390 395 400
Asp Gln Glu Val Met Glu Thr Asn Arg Val Glu Ser Val Glu Pro Ser
405 410 415
Glu Asn Glu Ala Ser Lys Glu Leu Glu Pro Glu Met Glu Phe Glu Ile
420 425 430
Glu Pro Asp Lys Glu Cys Lys Ser Leu Ser Pro Gly Lys Glu Asn Val
435 440 445
Ser Ala Leu Asp Met Glu Lys Glu Ser Asp Glu Lys Glu Glu Lys Glu
450 455 460
Ser Glu Pro Gln Pro Glu Pro Val Ala Gln Pro Gln Ala Gln Ser Gln
465 470 475 480
Pro Gln Leu Gln Leu Gln Ser Gln Ser Glu Pro Gln Pro Gln Leu Gln
485 490 495
Pro Glu Pro Ala Gln Pro Gln Leu Gln Ser Gln Pro Gln Leu Gln Leu
500 505 510
Gln Ser Gln Cys His Ala Val Leu Gln Ser His Pro Pro Ser Gln Pro
515 520 525
Glu Asp Leu Ser Leu Ala Val Leu Gln Pro Thr Pro Gln Val Thr Gln

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    530                 535                 540
Glu His Gly His Phe Leu Pro Glu Arg Lys Asp Phe Pro Val Glu Ser
545                 550                 555                 560
Val Lys Leu Thr Glu Val Pro Val Asp Pro Val Leu Thr Val His Pro
                565                 570                 575
Glu Ser Glu Ser Glu Thr Asn Thr Arg Ser Arg Ser Arg Gly Arg Thr
            580                 585                 590
Arg Asn Arg Thr Thr Lys Ser Arg Ser Arg Ser Ser Ser Ser Ser Ser
        595                 600                 605
Ser Ser Ser Ser Ser Thr Ser Ser Ser Ser Gly Ser Ser Ser Ser Ser
    610                 615                 620
Gly Ser Ser Ser Ser Arg Ser Ser Ser Ser Ser Ser Ser Ser Thr Ser
625                 630                 635                 640
Gly Ser Ser Ser Arg Asp Ser Ser Ser Ser Thr Ser Ser Ser Ser Glu
                645                 650                 655
Ser Arg Ser Arg Ser Arg Gly Arg Gly His Asn Arg Asp Arg Lys His
            660                 665                 670
Arg Arg Ser Val Asp Arg Lys Arg Arg Asp Thr Ser Gly Leu Glu Arg
        675                 680                 685
Ser His Lys Ser Ser Lys Gly Gly Ser Ser Arg Asp Thr Lys Gly Ser
    690                 695                 700
Lys Asp Lys Asn Ser Arg Ser Asp Arg Lys Arg Ser Ile Ser Glu Ser
705                 710                 715                 720
Ser Arg Ser Gly Lys Arg Ser Ser Arg Ser Glu Arg Asp Arg Lys Ser
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Asp Arg Lys Asp Lys Arg Arg
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<210> 189
<211> 1182
<212> DNA
<213> Homo sapiens

<400> 189

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gccaggtacc aatgggtgcg ctgcaatcca gacagtaatt ctgcaaactg ccttgaagaa 180
aaaggaccaa tgttcgaact acttccaggt gaatccaaca agatcccccg tctgaggact 240
gacctttttc caaagacgag aatccaggac ttgaatcgta tcttcccact ttctgaggac 300
tactctggat caggcttcgg ctccggctcc ggctctggat caggatctgg gagtggcttc 360
ctaacggaaa tggaacagga ttaccaacta gtagacgaaa gtgatgcttt ccatgacaac 420
cttaggtctc ttgacaggaa tctgccctca gacagccagg acttgggtca acatggatta 480
gaagaggatt ttatgttata aaagaggatt ttcccacctt gacaccaggc aatgtagtta 540
gcatatttta tgtaccatgg ttatatgatt aatcttggga caaagaattt tatagaaatt 600
tttaaacatc tgaaaaagaa gcttaagttt tatcatcctt ttttttctca tgaattctta 660
aaggattatg ctttaatgct gttatctatc ttattgttct tgaaaatacc tgcatttttt 720
ggtatcatgt tcaaccaaca tcattatgaa attaattaga ttcccatggc cataaaatgg 780
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gatgtgtttg tctacaagta tgattgctgt tacataacac cccaaattaa ctcccaaatt 1080
aaaacacagt tgtgctgtca atacctcata ctgctttacc ttttttttcct ggatatctgt 1140
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<210> 190
<211> 158
<212> PRT

<213> Homo sapiens

<400> 190
Met Met Gln Lys Leu Leu Lys Cys Ser Arg Leu Val Leu Ala Leu Ala
1 5 10 15
Leu Ile Leu Val Leu Glu Ser Ser Val Gln Gly Tyr Pro Thr Gln Arg
20 25 30
Ala Arg Tyr Gln Trp Val Arg Cys Asn Pro Asp Ser Asn Ser Ala Asn
35 40 45
Cys Leu Glu Glu Lys Gly Pro Met Phe Glu Leu Leu Pro Gly Glu Ser
50 55 60
Asn Lys Ile Pro Arg Leu Arg Thr Asp Leu Phe Pro Lys Thr Arg Ile
65 70 75 80
Gln Asp Leu Asn Arg Ile Phe Pro Leu Ser Glu Asp Tyr Ser Gly Ser
85 90 95
Gly Phe Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Phe
100 105 110
Leu Thr Glu Met Glu Gln Asp Tyr Gln Leu Val Asp Glu Ser Asp Ala
115 120 125
Phe His Asp Asn Leu Arg Ser Leu Asp Arg Asn Leu Pro Ser Asp Ser
130 135 140
Gln Asp Leu Gly Gln His Gly Leu Glu Glu Asp Phe Met Leu
145 150 155

<210> 191
<211> 1595
<212> DNA
<213> Homo sapiens

<400> 191
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cgtgtaaaca cactacttat cattgatgca tatataaaac cattttattt tcgctattat 180
ttcagaggaa gcgcctctga tttgtttctt ttttcccttt ttgctctttc tggctgtgtg 240
gtttggagaa agcacagttg gagtagccgg ttgctaaata agtcccgagc gcgagcggag 300
acgatgcagc ggagactggt tcagcagtgg agcgtcgcgg tgttcctgct gagctacgcg 360
gtgccctcct gcgggcgctc ggtggagggt ctcagccgcc gcctcaaaag agctgtgtct 420
gaacatcagc tcctccatga caaggggaag tccatccaag atttacggcg acgattcttc 480
cttcaccatc tgatcgcaga aatccacaca gctgaaatca gagctacctc ggaggtgtcc 540
cctaactcca agccctctcc caacacaaag aaccaccccg tccgatttgg gtctgatgat 600
gagggcagat acctaactca ggaaactaac aaggtggaga cgtacaaaga gcagccgctc 660
aagacacctg ggaagaaaaa gaaaggcaag cccgggaaac gcaaggagca ggaaaagaaa 720
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gatattatct acaaacactg cagaacagca tcatgtcata aacgattctg agccattcac 1320
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taaattatgt tttaaacaca tgccttaaat ttgtttaatt aaatttaact ctggtttcta 1440
ccagctcata caaaataaat ggtttctgaa aatgtttaag tattaactta caaggatata 1500
ggtttttctc atgtatcttt ttgttcattg gcaagatgaa ataatttttc tagggtaatg 1560
ccgtaggaaa aataaaactt cacatttaaa aaaaa 1595

<210> 192
<211> 175
<212> PRT
<213> Homo sapiens

<400> 192
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Ser Tyr Ala Val Pro Ser Cys Gly Arg Ser Val Glu Gly Leu Ser Arg
20 25 30
Arg Leu Lys Arg Ala Val Ser Glu His Gln Leu Leu His Asp Lys Gly
35 40 45
Lys Ser Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile
50 55 60
Ala Glu Ile His Thr Ala Glu Ile Arg Ala Thr Ser Glu Val Ser Pro
65 70 75 80
Asn Ser Lys Pro Ser Pro Asn Thr Lys Asn His Pro Val Arg Phe Gly
85 90 95
Ser Asp Asp Glu Gly Arg Tyr Leu Thr Gln Glu Thr Asn Lys Val Glu
100 105 110
Thr Tyr Lys Glu Gln Pro Leu Lys Thr Pro Gly Lys Lys Lys Lys Gly
115 120 125
Lys Pro Gly Lys Arg Lys Glu Gln Glu Lys Lys Lys Arg Arg Thr Arg
130 135 140
Ser Ala Trp Leu Asp Ser Gly Val Thr Gly Ser Gly Leu Glu Gly Asp
145 150 155 160
His Leu Ser Asp Thr Ser Thr Thr Ser Leu Glu Leu Asp Ser Arg
165 170 175

<210> 193
<211> 2657
<212> DNA
<213> Homo sapiens

<220>
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<222> 2623, 2624, 2625, 2626, 2627, 2628, 2629
<223> n = A,T,C or G

<400> 193
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actccatctt cgtgctcctc acaggccctg cctccctgcc tgctaaggac acagggaagg 120
gggtccccac ctcagtgcct gcctcccttc cctgtgcctg tgtacctggc agtcacagcc 180
acctggcgtg tcccagaaac caaccggctg acctcatctc ctgcccggcc ccacctccat 240
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cgggggcatt gcgaggcatc ccctccctgg gtttggctcc tgcccacggg gctgacagta 420
gaaatcacag gctgtgagac agctggagcc cagctctgct tgaacctatt ttaggtctct 480
gatccccgct tcctctttag actcccctag agctcagcca gtgctcaacc tgaggctggg 540
ggtctctgag gaagagtgag ttggagctga ggggtctggg gctgtcccct gagagagggg 600
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gcccctggcc cagcagccgc agctcccaac cacaatatcc tttggggttt ggcctacgga 720
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ggtcaggcat gcccctcctc atcgctggca cagcccagag ggtataaaca gtgctggagg 840
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ggaccctcat gataattttg tttctttcac tttctactct gttgacaacc attgtctcct 1080

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ttaacatccc taaaattttc cttacatgtt ttactagcca gatttttcct cctctcctga 2580
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ggcaggcatg caagctt                                                 2657
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<210> 194
<211> 168
<212> PRT
<213> Homo sapiens

<400> 194

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Met Gln Ala Gln Gln Tyr Gln Gln Gln Arg Arg Lys Phe Ala Ala Ala
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Phe Leu Ala Phe Ile Phe Ile Leu Ala Ala Val Asp Thr Ala Glu Ala
            20                  25                  30
Gly Lys Lys Glu Lys Pro Glu Lys Lys Val Lys Lys Ser Asp Cys Gly
        35                  40                  45
Glu Trp Gln Trp Ser Val Cys Val Pro Thr Ser Gly Asp Cys Gly Leu
    50                  55                  60
Gly Thr Arg Glu Gly Thr Arg Thr Gly Ala Glu Cys Lys Gln Thr Met
65                  70                  75                  80
Lys Thr Gln Arg Cys Lys Ile Pro Cys Asn Trp Lys Lys Gln Phe Gly
                85                  90                  95
Ala Glu Cys Lys Tyr Gln Phe Gln Ala Trp Gly Glu Cys Asp Leu Asn
            100                 105                 110
Thr Ala Leu Lys Thr Arg Thr Gly Ser Leu Lys Arg Ala Leu His Asn
        115                 120                 125
Ala Glu Cys Gln Lys Thr Val Thr Ile Ser Lys Pro Cys Gly Lys Leu
    130                 135                 140
Thr Lys Pro Lys Pro Gln Ala Glu Ser Lys Lys Lys Lys Lys Glu Gly
145                 150                 155                 160
Lys Lys Gln Glu Lys Met Leu Asp
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<210> 195

<211> 2972
<212> DNA
<213> Homo sapiens

<400> 195
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gacaagcagc aggttccatc tgaggacagt atggagaagg tgaaagtata cttgagggtt 240
aggcccttgt taccttcaga gttggaacga caggaagatc agggttgtgt ccgtattgag 300
aatgtggaga cccttgttct acaagcaccc aaggactcgt ttgccctgaa gagcaatgaa 360
cggggaattg gccaagccac acacaggttc acctttcccc agatctttgg gccagaagtg 420
ggacaggcat ccttcttcaa cctaactgtg aaggagatgg taaaggatgt actcaaaggg 480
cagaactggc tcatctatac atatggagtc actaactcag ggaaaaccca cacgattcaa 540
ggtaccatca aggatggagg gattctcccc cggtccctgg cgctgatctt caatagcctc 600
caaggccaac ttcatccaac acctgatctg aagcccttgc tctccaatga ggtaatctgg 660
ctagacagca agcagatccg acaggaggaa atgaagaagc tgtccctgct aaatggaggc 720
ctccaagagg aggagctgtc cacttccttg aagaggagtg tctacatcga aagtcggata 780
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agcagtagcc agctggatga aacaagtcat cgatgggcac agccagacac tgccccacta 900
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ctgctttatg acctattaga accgcctagc caacagcgca agaggcagac tttgcggcta 1020
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gctgaggagg cctggaagct cctaaaagtg ggtcgtaaga accagagctt tgccagcacc 1140
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gaagctctct tgcaggaagc cagacaacag tcagtggccc atcagcaatc agggtctgaa 2040
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aagaagttag aagagggcca gaagaatata aggctgttgc ggacagagct tcagaaactt 2280
ggtgagtctc tccaatcagc agagagagct tgttgccaca gcactggggc aggaaaactt 2340
cgtcaagcct tgaccacttg tgatgacatc ttaatcaaac aggaccagac tctggctgaa 2400
ctgcagaaca acatggtgct agtgaaactg gaccttcgga agaaggcagc atgtattgct 2460
gagcagtatc atactgtgtt gaaactccaa ggccaggttt ctgccaaaaa gcgccttggt 2520
accaaccagg aaaatcagca accaaaccaa caaccaccag ggaagaaacc attccttcga 2580
aatttacttc cccgaacacc aacctgccaa agctcaacag actgcagccc ttatgcccgg 2640
atcctacgct cacggcgttc ccctttactc aaatctgggc cttttggcaa aaagtactaa 2700
ggctgtgggg aaagagaaga gcagtcatgg ccctgaggtg ggtcagctac tctcctgaag 2760
aaataggtct cttttatgct ttaccatata tcaggaatta tatccaggat gcaatactca 2820
gacactagct tttttctcac ttttgtatta taaccaccta tgtaatctca tgttgttgtt 2880
ttttttttatt tacttatatg atttctatgc acacaaaaac agttatatta aagatattat 2940
tgttcacatt ttttattgaa aaaaaaaaaa aa 2972

<210> 196
<211> 890
<212> PRT

<213> Homo sapiens

<400> 196
Met Ser Gln Gly Ile Leu Ser Pro Pro Ala Gly Leu Leu Ser Asp Asp
1 5 10 15
Asp Val Val Val Ser Pro Met Phe Glu Ser Thr Ala Ala Asp Leu Gly
20 25 30
Ser Val Val Arg Lys Asn Leu Leu Ser Asp Cys Ser Val Val Ser Thr
35 40 45
Ser Leu Glu Asp Lys Gln Gln Val Pro Ser Glu Asp Ser Met Glu Lys
50 55 60
Val Lys Val Tyr Leu Arg Val Arg Pro Leu Leu Pro Ser Glu Leu Glu
65 70 75 80
Arg Gln Glu Asp Gln Gly Cys Val Arg Ile Glu Asn Val Glu Thr Leu
85 90 95
Val Leu Gln Ala Pro Lys Asp Ser Phe Ala Leu Lys Ser Asn Glu Arg
100 105 110
Gly Ile Gly Gln Ala Thr His Arg Phe Thr Phe Ser Gln Ile Phe Gly
115 120 125
Pro Glu Val Gly Gln Ala Ser Phe Phe Asn Leu Thr Val Lys Glu Met
130 135 140
Val Lys Asp Val Leu Lys Gly Gln Asn Trp Leu Ile Tyr Thr Tyr Gly
145 150 155 160
Val Thr Asn Ser Gly Lys Thr His Thr Ile Gln Gly Thr Ile Lys Asp
165 170 175
Gly Gly Ile Leu Pro Arg Ser Leu Ala Leu Ile Phe Asn Ser Leu Gln
180 185 190
Gly Gln Leu His Pro Thr Pro Asp Leu Lys Pro Leu Leu Ser Asn Glu
195 200 205
Val Ile Trp Leu Asp Ser Lys Gln Ile Arg Gln Glu Glu Met Lys Lys
210 215 220
Leu Ser Leu Leu Asn Gly Gly Leu Gln Glu Glu Glu Leu Ser Thr Ser
225 230 235 240
Leu Lys Arg Ser Val Tyr Ile Glu Ser Arg Ile Gly Thr Ser Thr Ser
245 250 255
Phe Asp Ser Gly Ile Ala Gly Leu Ser Ser Ile Ser Gln Cys Thr Ser
260 265 270
Ser Ser Gln Leu Asp Glu Thr Ser His Arg Trp Ala Gln Pro Asp Thr
275 280 285
Ala Pro Leu Pro Val Pro Ala Asn Ile Arg Phe Ser Ile Trp Ile Ser
290 295 300
Phe Phe Glu Ile Tyr Asn Glu Leu Leu Tyr Asp Leu Leu Glu Pro Pro
305 310 315 320
Ser Gln Gln Arg Lys Arg Gln Thr Leu Arg Leu Cys Glu Asp Gln Asn
325 330 335
Gly Asn Pro Tyr Val Lys Asp Leu Asn Trp Ile His Val Gln Asp Ala
340 345 350
Glu Glu Ala Trp Lys Leu Leu Lys Val Gly Arg Lys Asn Gln Ser Phe
355 360 365
Ala Ser Thr His Leu Asn Gln Asn Ser Ser Arg Ser His Ser Ile Phe
370 375 380
Ser Ile Arg Ile Leu His Leu Gln Gly Glu Gly Asp Ile Val Pro Lys
385 390 395 400
Ile Ser Glu Leu Ser Leu Cys Asp Leu Ala Gly Ser Glu Arg Cys Lys
405 410 415
Asp Gln Lys Ser Gly Glu Arg Leu Lys Glu Ala Gly Asn Ile Asn Thr
420 425 430
Ser Leu His Thr Leu Gly Arg Cys Ile Ala Ala Leu Arg Gln Asn Gln
435 440 445

Gln Asn Arg Ser Lys Gln Asn Leu Val Pro Phe Arg Asp Ser Lys Leu
    450   455   460
Thr Arg Val Phe Gln Gly Phe Phe Thr Gly Arg Gly Arg Ser Cys Met
465   470   475   480
Ile Val Asn Val Asn Pro Cys Ala Ser Thr Tyr Asp Glu Thr Leu His
                485   490   495
Val Ala Lys Phe Ser Ala Ile Ala Ser Gln Leu Val His Ala Pro Pro
            500   505   510
Met Gln Leu Gly Phe Pro Ser Leu His Ser Phe Ile Lys Glu His Ser
        515   520   525
Leu Gln Val Ser Pro Ser Leu Glu Lys Gly Ala Lys Ala Asp Thr Gly
    530   535   540
Leu Asp Asp Asp Ile Glu Asn Glu Ala Asp Ile Ser Met Tyr Gly Lys
545   550   555   560
Glu Glu Leu Leu Gln Val Val Glu Ala Met Lys Thr Leu Leu Leu Lys
                565   570   575
Glu Arg Gln Glu Lys Leu Gln Leu Glu Met His Leu Arg Asp Glu Ile
            580   585   590
Cys Asn Glu Met Val Glu Gln Met Gln Gln Arg Glu Gln Trp Cys Ser
        595   600   605
Glu His Leu Asp Thr Gln Lys Glu Leu Leu Glu Glu Met Tyr Glu Glu
    610   615   620
Lys Leu Asn Ile Leu Lys Glu Ser Leu Thr Ser Phe Tyr Gln Glu Glu
625   630   635   640
Ile Gln Glu Arg Asp Glu Lys Ile Glu Glu Leu Glu Ala Leu Leu Gln
                645   650   655
Glu Ala Arg Gln Gln Ser Val Ala His Gln Gln Ser Gly Ser Glu Leu
            660   665   670
Ala Leu Arg Arg Ser Gln Arg Leu Ala Ala Ser Ala Ser Thr Gln Gln
        675   680   685
Leu Gln Glu Val Lys Ala Lys Leu Gln Gln Cys Lys Ala Glu Leu Asn
    690   695   700
Ser Thr Thr Glu Glu Leu His Lys Tyr Gln Lys Met Leu Glu Pro Pro
705   710   715   720
Pro Ser Ala Lys Pro Phe Thr Ile Asp Val Asp Lys Lys Leu Glu Glu
                725   730   735
Gly Gln Lys Asn Ile Arg Leu Leu Arg Thr Glu Leu Gln Lys Leu Gly
            740   745   750
Glu Ser Leu Gln Ser Ala Glu Arg Ala Cys Cys His Ser Thr Gly Ala
        755   760   765
Gly Lys Leu Arg Gln Ala Leu Thr Thr Cys Asp Asp Ile Leu Ile Lys
    770   775   780
Gln Asp Gln Thr Leu Ala Glu Leu Gln Asn Asn Met Val Leu Val Lys
785   790   795   800
Leu Asp Leu Arg Lys Lys Ala Ala Cys Ile Ala Glu Gln Tyr His Thr
                805   810   815
Val Leu Lys Leu Gln Gly Gln Val Ser Ala Lys Lys Arg Leu Gly Thr
            820   825   830
Asn Gln Glu Asn Gln Gln Pro Asn Gln Gln Pro Pro Gly Lys Lys Pro
        835   840   845
Phe Leu Arg Asn Leu Leu Pro Arg Thr Pro Thr Cys Gln Ser Ser Thr
    850   855   860
Asp Cys Ser Pro Tyr Ala Arg Ile Leu Arg Ser Arg Arg Ser Pro Leu
865   870   875   880
Leu Lys Ser Gly Pro Phe Gly Lys Lys Tyr
                885   890

<210> 197

<211> 768
<212> DNA
<213> Homo sapiens

<400> 197
ccttcagcat aaaagctgat ccacaaacaa gaggagcacc agacctcctc ttggcttcga 60
gatggcttcg ccacaccaag agcccaaacc tggagacctg attgagattt tccgccttgg 120
ctatgagcac tgggccctgt atataggaga tggctacgtg atccatctgg ctcctccaag 180
tgagtacccc ggggctggct cctccagtgt cttctcagtc ctgagcaaca gtgcagaggt 240
gaaacggggg cgcctggaag atgtggtggg aggctgttgc tatcgggtca acaacagctt 300
ggaccatgag taccaaccac ggcccgtgga ggtgatcatc agttctgcga aggagatggt 360
tggtcagaag atgaagtaca gtattgtgag caggaactgt gagcactttg tcgcccagct 420
gagatatggc aagtcccgct gtaaacaggt ggaaaaggcc aaggttgaag tcggtgtggc 480
cacggcgctt ggaatcctgg ttgttgctgg atgctctttt gcgattagga gataccaaaa 540
aaaagcaaca gcctgaagca gccacaaaat cctgtgttag aagcagctgt gggggtccca 600
gtggagatga gcctccccca tgcctccagc agcctgaccc tcgtgccctg tctcaggcgt 660
tctctagatc ctttcctctg tttccctctc tcgctggcaa aagtatgatc taattgaaac 720
aagactgaag gatcaataaa cagccatctg ccccttcaaa aaaaaaaa 768

<210> 198
<211> 164
<212> PRT
<213> Homo sapiens

<400> 198
Met Ala Ser Pro His Gln Glu Pro Lys Pro Gly Asp Leu Ile Glu Ile
1 5 10 15
Phe Arg Leu Gly Tyr Glu His Trp Ala Leu Tyr Ile Gly Asp Gly Tyr
20 25 30
Val Ile His Leu Ala Pro Pro Ser Glu Tyr Pro Gly Ala Gly Ser Ser
35 40 45
Ser Val Phe Ser Val Leu Ser Asn Ser Ala Glu Val Lys Arg Gly Arg
50 55 60
Leu Glu Asp Val Val Gly Gly Cys Cys Tyr Arg Val Asn Asn Ser Leu
65 70 75 80
Asp His Glu Tyr Gln Pro Arg Pro Val Glu Val Ile Ile Ser Ser Ala
85 90 95
Lys Glu Met Val Gly Gln Lys Met Lys Tyr Ser Ile Val Ser Arg Asn
100 105 110
Cys Glu His Phe Val Ala Gln Leu Arg Tyr Gly Lys Ser Arg Cys Lys
115 120 125
Gln Val Glu Lys Ala Lys Val Glu Val Gly Val Ala Thr Ala Leu Gly
130 135 140
Ile Leu Val Val Ala Gly Cys Ser Phe Ala Ile Arg Arg Tyr Gln Lys
145 150 155 160
Lys Ala Thr Ala

<210> 199
<211> 720
<212> DNA
<213> Homo sapiens

<400> 199
gggggggggc ggagggcgct catttccggg ccgcccacca cccgcgtagc accggcagcc 60
gctgtcccgg cagtctccag ccgtcccgcc cgcttgtggc caaactggct ccagtcactc 120
ccgaaatgcc agtcgacttc actgggtact ggaagatgtt ggtcaacgag aatttcgagg 180
agtacctgcg cgccctcgac gtcaatgtgg ccttgcgcaa aatcgccaac ttgctgaagc 240

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cagacaaaga gatcgtgcag gacggtgacc atatgatcat ccgcacgctg agcactttta 300
ggaactacat catggacttc caagttggga aggagtttga ggaggatctg acaggcatag 360
atgaccgcaa gtgcatgaca acagtgagct gggacggaga caagctccag tgtgtgcaga 420
agggtgagaa ggaggggcgt ggctggaccc agtggatcga gggtgatgag ctgcacctag 480
agatgagagt ggaaggtgtg gtctgcaagc aagtattcaa gaaggtgcag tgaggcccaa 540
gcagacaacc ttgtcccaac caatcagcag gatgtgtgag ccaggatccc tctttgcaca 600
gcatgaggca aaaatgtcca gccaccccta ggcatctgtt agcagagtct gtctcttggc 660
tttgtcactt ttccttttct taaaacaaag ccatgccaat aaagtgacct gtgttcaaaa 720


<210> 200
<211> 135
<212> PRT
<213> Homo sapiens

<400> 200
Met Pro Val Asp Phe Thr Gly Tyr Trp Lys Met Leu Val Asn Glu Asn
1               5                   10                  15
Phe Glu Glu Tyr Leu Arg Ala Leu Asp Val Asn Val Ala Leu Arg Lys
            20                  25                  30
Ile Ala Asn Leu Leu Lys Pro Asp Lys Glu Ile Val Gln Asp Gly Asp
        35                  40                  45
His Met Ile Ile Arg Thr Leu Ser Thr Phe Arg Asn Tyr Ile Met Asp
    50                  55                  60
Phe Gln Val Gly Lys Glu Phe Glu Glu Asp Leu Thr Gly Ile Asp Asp
65                  70                  75                  80
Arg Lys Cys Met Thr Thr Val Ser Trp Asp Gly Asp Lys Leu Gln Cys
                85                  90                  95
Val Gln Lys Gly Glu Lys Glu Gly Arg Gly Trp Thr Gln Trp Ile Glu
            100                 105                 110
Gly Asp Glu Leu His Leu Glu Met Arg Val Glu Gly Val Val Cys Lys
        115                 120                 125
Gln Val Phe Lys Lys Val Gln
    130                 135


<210> 201
<211> 2383
<212> DNA
<213> Homo sapiens

<400> 201
ggggctaccg cgcctttgct tcctggcgca cgcggagcct cctggagcct gccaccatcc 60
tgcctactac gtgctgccct gcgcccgcag ccatgtgccg caccctggcc gccttcccca 120
ccacctgcct ggagagagcc aaagagttca agacacgtct ggggatcttt cttcacaaat 180
cagagctggg ctgcgatact gggagtactg gcaagtccga gtggggcagt aaacacagca 240
aagagaatag aaacttctca gaagatgtgc tggggtggag agagtcgttc gacctgctgc 300
tgagcagtaa aaatggagtg gctgccttcc acgctttcct gaagacagag ttcagtgagg 360
agaacctgga gttctggctg gcctgtgagg agttcaagaa gatccgatca gctaccaagc 420
tggcctccag ggcacaccag atctttgagg agttcatttg cagtgaggcc cctaaagagg 480
tcaacattga ccatgagacc cgcgagctga cgaggatgaa cctgcagact gccacagcca 540
catgctttga tgcggctcag gggaagacac gtaccctgat ggagaaggac tcctacccac 600
gcttcctgaa gtcgcctgct taccgggacc tggctgccca agcctcagcc gcctctgcca 660
ctctgtccag ctgcagcctg gacgagccct cacacacctg agtctccacg gcagtgagga 720
agccagccgg gaagagaggt tgagtcaccc atccccgagg tggctgcccc tgtgtgggag 780
gcaggttctg caaagcaagt gcaagaggac aaaaaaaaaa aaaaaaaaaa aaaaaatgcg 840
ctccagcagc ctgtttggga agcagcagtc tctccttcag atactgtggg actcatgctg 900
gagaggagcc gcccacttcc aggacctgtg aataagggct aatgatgagg gttggtgggg 960
ctctctgtgg ggcaaaaagg tggtatgggg gttagcactg gctctcgttc tcaccggaga 1020
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aggaagtgtt ctagtgtggt ttaggaaaca tgtggataaa gggaaccatg aaaatgagag 1080
gaggaaagac atccagatca gctgttttgc ctgttgctca gttgactctg attgcatcct 1140
gttttcctaa ttcccagact gttctgggca cggaagggac cctggatgtg gagtcttccc 1200
ctttggccct cctcactggc ctctgggcta gcccagagtc ccttagcttg tacctcgtaa 1260
cactcctgtg tgtctgtcca gccttgcagt catgtcaagg ccagcaagct gatgtgactc 1320
ttgccccatg cgagatattt atacctcaaa cactggcctg tgagcccttt ccaagtcagt 1380
ggagagccct gaaaggaggc tcacttgaat ccagctcagt gctctgggtg gccccctgca 1440
ggtggcccct gaccctgcgt tgcagcaggg tccacctgtg agcaggcccg ccctggggcc 1500
tcttcctgga tgtgccctct ctgagttctg tgctgtctct tggaggcagg gcccaggaga 1560
acaaagtgtg gaggcctcgg ggagtggctt ttccagctct catgccccgc agtgtggaac 1620
aaggcagaaa aggatcctag gaaataagtc tcttggcggt ccctgagagt cctgctgaaa 1680
tccagccagt gtttttgtg gtatgagaac aggcaaaaag agatgccccg agatagaagg 1740
ggagccttgt gtttctttcc tgcagacgtg agatgaacac tggagtgggc agaggtggcm 1800
caggaccatg gcaccottag agtgcagaag ctgggggag aggctgcttc gaagggcagg 1860
actggggata cctgcctgtc acctcagggc atcactgaac aaacatttcc tgatggsaac 1920
tcctgcggca gagcccaggc tggggaagtg aactacccag ggcagcccct ttgtggccca 1980
ggataatcaa cactgttctc tctgtaccat gagctcctcc aggagattat ttaagtgtat 2040
tgtatcattg gttttctgtg attgtcataa cattgttttt gttattgttg gtgctgttgt 2100
tatttattat tgtaatttca gtttgcctct actggagaat ctcagcaggg gtttcagcct 2160
gactgtctcc ctttctctac cagactctac ctctgaatgt gctgggaacc tcttggagcc 2220
tgtcaggaac tcctcactgt ttaaatattt atttattgtg acaaatggag ctggtttcct 2280
agatatgaat gatgtttgca atccccattt tcctgtttca gcatgttata ttcttataaa 2340
ataaaagcaa aagtcaaata tgaaaaaaaa aaaaaaaaaa aaa 2383

<210> 202
<211> 202
<212> PRT
<213> Homo sapiens

<400> 202
Met Cys Arg Thr Leu Ala Ala Phe Pro Thr Thr Cys Leu Glu Arg Ala
1 5 10 15
Lys Glu Phe Lys Thr Arg Leu Gly Ile Phe Leu His Lys Ser Glu Leu
20 25 30
Gly Cys Asp Thr Gly Ser Thr Gly Lys Ser Glu Trp Gly Ser Lys His
35 40 45
Ser Lys Glu Asn Arg Asn Phe Ser Glu Asp Val Leu Gly Trp Arg Glu
50 55 60
Ser Phe Asp Leu Leu Leu Ser Ser Lys Asn Gly Val Ala Ala Phe His
65 70 75 80
Ala Phe Leu Lys Thr Glu Phe Ser Glu Glu Asn Leu Glu Phe Trp Leu
85 90 95
Ala Cys Glu Glu Phe Lys Lys Ile Arg Ser Ala Thr Lys Leu Ala Ser
100 105 110
Arg Ala His Gln Ile Phe Glu Glu Phe Ile Cys Ser Glu Ala Pro Lys
115 120 125
Glu Val Asn Ile Asp His Glu Thr Arg Glu Leu Thr Arg Met Asn Leu
130 135 140
Gln Thr Ala Thr Ala Thr Cys Phe Asp Ala Ala Gln Gly Lys Thr Arg
145 150 155 160
Thr Leu Met Glu Lys Asp Ser Tyr Pro Arg Phe Leu Lys Ser Pro Ala
165 170 175
Tyr Arg Asp Leu Ala Ala Gln Ala Ser Ala Ala Ser Ala Thr Leu Ser
180 185 190
Ser Cys Ser Leu Asp Glu Pro Ser His Thr
195 200

<210> 203

<211> 616
<212> DNA
<213> Homo sapiens

<400> 203
ctcccctggg agcctggctg ccttgctctc cttcctgggt ctgtctctgc cacctggtct 60
gccacagatc catgatgtgc agttctctgg agcaggcgct ggctgtgctg gtcactacct 120
tccacaagta ctcctgccaa gagggcgaca agttcaagct gagtaagggg gaaatgaagg 180
aacttctgca caaggagctg cccagctttg tggggcattc cagagaacca tgtgctgtga 240
gggccttccg agtccatctg tttaatcctg tcattggaga cttgagaaac cagagcccag 300
aagggaaaag tgattgtccc aagatcacac agcactggag aaagtggatg aggaggggct 360
gaagaagctg atgggcagcc tggatgagaa cagtgaccag caggtggact tccaggagta 420
tgctgttttc ctggcactca tcactgtcat gtgcaatgac ttcttccagg gctgcccaga 480
ccgaccctga agcagaactc ttgacttcct gccatggatc tcttgggccc aggactgttg 540
atgcctttga gttttgtatt caataaactt tttttgtctg ttgaaaaaaa aaaaaaaaaa 600
aaaaaaaaaa aaaaaa 616

<210> 204
<211> 96
<212> PRT
<213> Homo sapiens

<400> 204
Met Met Cys Ser Ser Leu Glu Gln Ala Leu Ala Val Leu Val Thr Thr
1 5 10 15
Phe His Lys Tyr Ser Cys Gln Glu Gly Asp Lys Phe Lys Leu Ser Lys
20 25 30
Gly Glu Met Lys Glu Leu Leu His Lys Glu Leu Pro Ser Phe Val Gly
35 40 45
His Ser Arg Glu Pro Cys Ala Val Arg Ala Phe Arg Val His Leu Phe
50 55 60
Asn Pro Val Ile Gly Asp Leu Arg Asn Gln Ser Pro Glu Gly Lys Ser
65 70 75 80
Asp Cys Pro Lys Ile Thr Gln His Trp Arg Lys Trp Met Arg Arg Gly
85 90 95

<210> 205
<211> 428
<212> DNA
<213> Homo sapiens

<400> 205
ctgggtctgt ctctgccacc tggtctgcca cagatccatg atgtgcagtt ctctggagca 60
ggcgctggct gtgctggtca ctaccttcca caagtactcc tgccaagagg gcgacaagtt 120
caagctgagt aagggggaaa tgaaggaact tctgcacaag gagctgccca gctttgtggg 180
gcattccaga gaaccatgtg ctgtgagggc cttccgagtc catctgttta atcctgtcat 240
tggagacttg agaaaccaga gcccagaagg gaaaagtgat tgtcccaaga tcacacagca 300
ctggagaaag tggatgagga ggggctgaag aagctgatgg gcagcctgga tgagaacagt 360
gaccagcagg tggacttcca ggagtatgct gttttcctgg cactcatcac tgtcatgtgc 420
aatgacttc 428

<210> 206
<211> 97
<212> PRT
<213> Homo sapiens

<400> 206
Met Cys Ser Ser Leu Glu Gln Ala Leu Ala Val Leu Val Thr Thr Phe

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1               5                   10                  15
His Lys Tyr Ser Cys Gln Glu Gly Asp Lys Phe Lys Leu Ser Lys Gly
                20                  25                  30
Glu Met Lys Glu Leu Leu His Lys Glu Leu Pro Ser Phe Val Gly Glu
        35                  40                  45
Lys Val Asp Glu Glu Gly Leu Lys Lys Leu Met Gly Ser Leu Asp Glu
    50                  55                  60
Asn Ser Asp Gln Gln Val Asp Phe Gln Glu Tyr Ala Val Phe Leu Ala
65                  70                  75                  80
Leu Ile Thr Val Met Cys Asn Asp Phe Phe Gln Gly Cys Pro Asp Arg
                85                  90                  95
Pro
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<210> 207
<211> 799
<212> DNA
<213> Homo sapiens

<400> 207

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cactcccaaa gaactgggta ctcaacactg agcagatctg ttctttgagc taaaaaccat 60
gtgctgtacc aagagtttgc tcctggctgc tttgatgtca gtgctgctac tccacctctg 120
cggcgaatca gaagcagcaa gcaactttga ctgctgtctt ggatacacag accgtattct 180
tcatcctaaa tttattgtgg gcttcacacg gcagctggcc aatgaaggct gtgacatcaa 240
tgctatcatc tttcacacaa agaaaaagtt gtctgtgtgc gcaaatccaa aacagacttg 300
ggtgaaatat attgtgcgtc tcctcagtaa aaaagtcaag aacatgtaaa aactgtggct 360
tttctggaat ggaattggac atagcccaag aacagaaaga accttgctgg ggttggaggt 420
ttcacttgca catcatggag ggtttagtgc ttatctaatt tgtgcctcac tggacttgtc 480
caattaatga agttgattca tattgcatca tagtttgctt tgtttaagca tcacattaaa 540
gttaaactgt attttatgtt atttatagct gtaggttttc tgtgtttagc tatttaatac 600
taattttcca taagctattt tggtttagtg caaagtataa aattatattt ggggggggaat 660
aagattatat ggactttctt gcaagcaaca agctattttt taaaaaaact atttaacatt 720
cttttgttta tattgttttg tctcctaaat tgttgtaatt gcattataaa ataagaaaaa 780
cattaataag acaaatatt                                              799
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<210> 208
<211> 96
<212> PRT
<213> Homo sapiens

<400> 208

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Met Cys Cys Thr Lys Ser Leu Leu Leu Ala Ala Leu Met Ser Val Leu
1               5                   10                  15
Leu Leu His Leu Cys Gly Glu Ser Glu Ala Ala Ser Asn Phe Asp Cys
                20                  25                  30
Cys Leu Gly Tyr Thr Asp Arg Ile Leu His Pro Lys Phe Ile Val Gly
        35                  40                  45
Phe Thr Arg Gln Leu Ala Asn Glu Gly Cys Asp Ile Asn Ala Ile Ile
    50                  55                  60
Phe His Thr Lys Lys Lys Leu Ser Val Cys Ala Asn Pro Lys Gln Thr
65                  70                  75                  80
Trp Val Lys Tyr Ile Val Arg Leu Leu Ser Lys Lys Val Lys Asn Met
                85                  90                  95
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<210> 209
<211> 2133
<212> DNA

<213> Homo sapiens

<400> 209
cgggagagcg cgctctgcct gccgcctgcc tgcctgccac tgagggttcc cagcaccatg 60
agggcctgga tcttctttct cctttgcctg gccgggaggg ccttggcagc ccctcagcaa 120
gaagccctgc ctgatgagac agaggtggtg gaagaaactg tggcagaggt gactgaggta 180
tctgtgggag ctaatcctgt ccaggtggaa gtaggagaat ttgatgatgg tgcagaggaa 240
accgaagagg aggtggtggc ggaaaatccc tgccagaacc accactgcaa acacggcaag 300
gtgtgcgagc tggatgagaa caacaccccc atgtgcgtgt gccaggaccc caccagctgc 360
ccagccccca ttggcgagtt tgagaaggtg tgcagcaatg acaacaagac cttcgactct 420
tcctgccact tctttgccac aaagtgcacc ctggagggca ccaagaaggg ccacaagctc 480
cacctggact acatcgggcc ttgcaaatac atcccccctt gcctggactc tgagctgacc 540
gaattccccc tgcgcatgcg ggactggctc aagaacgtcc tggtcaccct gtatgagagg 600
gatgaggaca acaaccttct gactgagaag cagaagctgc gggtgaagaa gatccatgag 660
aatgagaagc gcctggaggc aggagaccac cccgtggagc tgctggcccg ggacttcgag 720
aagaactata acatgtacat cttccctgta cactggcagt tcggccagct ggaccagcac 780
cccattgacg ggtacctctc ccacaccgag ctggctccac tgcgtgctcc cctcatcccc 840
atggagcatt gcaccacccg ctttttcgag acctgtgacc tggacaatga caagtacatc 900
gccctggatg agtgggccgg ctgcttcggc atcaagcaga aggatatcga caaggatctt 960
gtgatctaaa tccactcctt ccacagtacc ggattctctc tttaaccctc cccttcgtgt 1020
ttcccccaat gtttaaaatg tttggatggt ttgttgttct gcctggagac aaggtgctaa 1080
catagattta agtgaataca ttaacggtgc taaaaatgaa aattctaacc caagacatga 1140
cattcttagc tgtaacttaa ctattaaggc cttttccaca cgcattaata gtcccatttt 1200
tctcttgcca tttgtagctt tgcccattgt cttattggca catgggtgga cacggatctg 1260
ctgggctctg ccttaaacac acattgcagc ttcaactttt ctctttagtg ttctgtttga 1320
aactaatact taccgagtca gactttgtgt tcatttcatt tcagggtctt ggctgcctgt 1380
gggcttcccc aggtggcctg gaggtgggca aagggaagta acagacacac gatgttgtca 1440
aggatggttt tgggactaga ggctcagtgg tgggagagat ccctgcagaa tccaccaacc 1500
agaacgtggt ttgcctgagg ctgtaactga gagaaagatt ctggggctgt cttatgaaaa 1560
tatagacatt ctcacataag cccagttcat caccatttcc tcctttacct ttcagtgcag 1620
tttcttttca cattaggctg ttggttcaaa cttttgggag cacggactgt cagttctctg 1680
ggaagtggtc agcgcatcct gcagggcttc tcctcctctg tcttttggag aaccagggct 1740
cttctcaggg gctctaggga ctgccaggct gtttcagcca ggaaggccaa aatcaagagt 1800
gagatgtaga aagttgtaaa atagaaaaag tggagttggt gaatcggttg ttctttcctc 1860
acatttggat gattgtcata aggtttttag catgttcctc cttttcttca ccctcccctt 1920
tgttcttcta ttaatcaaga gaaacttcaa agttaatggg atggtcggat ctcacaggct 1980
gagaactcgt tcacctccaa gcatttcatg aaaaagctgc ttcttattaa tcatacaaac 2040
tctcaccatg atgtgaagag tttcacaaat ctttcaaaat aaaaagtaat gacttagaaa 2100
ctgaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 2133

<210> 210
<211> 303
<212> PRT
<213> Homo sapiens

<400> 210
Met Arg Ala Trp Ile Phe Phe Leu Leu Cys Leu Ala Gly Arg Ala Leu
1 5 10 15
Ala Ala Pro Gln Gln Glu Ala Leu Pro Asp Glu Thr Glu Val Val Glu
20 25 30
Glu Thr Val Ala Glu Val Thr Glu Val Ser Val Gly Ala Asn Pro Val
35 40 45
Gln Val Glu Val Gly Glu Phe Asp Asp Gly Ala Glu Glu Thr Glu Glu
50 55 60
Glu Val Val Ala Glu Asn Pro Cys Gln Asn His His Cys Lys His Gly
65 70 75 80
Lys Val Cys Glu Leu Asp Glu Asn Asn Thr Pro Met Cys Val Cys Gln
85 90 95
Asp Pro Thr Ser Cys Pro Ala Pro Ile Gly Glu Phe Glu Lys Val Cys

```
                100                 105                 110
Ser Asn Asp Asn Lys Thr Phe Asp Ser Ser Cys His Phe Phe Ala Thr
            115                 120                 125
Lys Cys Thr Leu Glu Gly Thr Lys Lys Gly His Lys Leu His Leu Asp
        130                 135                 140
Tyr Ile Gly Pro Cys Lys Tyr Ile Pro Pro Cys Leu Asp Ser Glu Leu
145                 150                 155                 160
Thr Glu Phe Pro Leu Arg Met Arg Asp Trp Leu Lys Asn Val Leu Val
                165                 170                 175
Thr Leu Tyr Glu Arg Asp Glu Asp Asn Asn Leu Leu Thr Glu Lys Gln
            180                 185                 190
Lys Leu Arg Val Lys Lys Ile His Glu Asn Glu Lys Arg Leu Glu Ala
        195                 200                 205
Gly Asp His Pro Val Glu Leu Leu Ala Arg Asp Phe Glu Lys Asn Tyr
    210                 215                 220
Asn Met Tyr Ile Phe Pro Val His Trp Gln Phe Gly Gln Leu Asp Gln
225                 230                 235                 240
His Pro Ile Asp Gly Tyr Leu Ser His Thr Glu Leu Ala Pro Leu Arg
                245                 250                 255
Ala Pro Leu Ile Pro Met Glu His Cys Thr Thr Arg Phe Phe Glu Thr
            260                 265                 270
Cys Asp Leu Asp Asn Asp Lys Tyr Ile Ala Leu Asp Glu Trp Ala Gly
        275                 280                 285
Cys Phe Gly Ile Lys Gln Lys Asp Ile Asp Lys Asp Leu Val Ile
    290                 295                 300
```

<210> 211
<211> 2228
<212> DNA
<213> Homo sapiens

<400> 211

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ggtacagtca tcacaagcct gttcggcggg actgtgatgg ccagagagat gacgatctta 60
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cctactccta aagtgattgg tattgatctt ggcaccacct attgttctgt tggggtgttt 180
tttcctggca caggaaaagt aaaggtgatt ccagatgaaa atgggcatat cagcataccc 240
agcatggtgt cttttactga caatgatgta tatgtgggat atgaaagcgt agagctggca 300
gattcaaatc ctcaaaacac aatatatgat gccaaaagat tcataggcaa gatttttacc 360
gcagaagagt tggaggctga aattggcaga tacccattta aggttttaaa caaaaatgga 420
atggttgagt tttctgtgac aagtaatgag accatcacag tgtccccaga atatgttggc 480
tctcgactat tgttgaagtt aaaggaaatg gcagaggcat atcttggaat gccagttgcc 540
aatgctgtca tttctgtacc agcagaattt gatctaaaac agagaaattc aacaattgaa 600
gctgctaacc ttgcaggact gaagattttg agggtaataa atgaacccac agcagcagct 660
atggcctatg gtctccacaa ggctgacgtc ttccacgtct tggtgataga cttgggcgga 720
ggaactctag atgtgtcttt actgaataaa caaggaggga tgtttctaac ccgagcaatg 780
tctggaaaca ataaacttgg aggacaggac ttcaatcaga gattgcttca gtacttatat 840
aaacagatct atcaaacata tggcttcgtg ccctctagga aagaggaaat ccacagattg 900
agacaagctg tggaaatggt caaattaaat ctgactcttc atcaatctgc tcagttgtca 960
gtattactaa cggtggagga gcaggacagg aaggaacctc acagtagtga cactgaactg 1020
ccaaaagaca aactttcctc agcagatgac catcgcgtga acagtgggtt tggacgtggc 1080
ctttctgata agaaaagtgg agaaagtcag gttttatttg aaacagaaat atcacggaaa 1140
ctctttgata cccttaatga agacctcttt cagaaaatac tggtacccat tcagcaagta 1200
ttgaaagaag gccacctgga aaagactgag attgatgagg tggttttagt tgggggctcc 1260
actcgtattc ctcggatccg tcaagtcatt caagagttct ttggaaaaga tcccaacaca 1320
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ggctcttggc ctctccaagt cagtgcttta gaaattccca ataagcattt acaaaaaacc 1440
aacttcaact gaattctgca gaaataatgg ttatttgtga acttgtctga tgatctcttc 1500
ccatttatca gattaccttt tccacaaaag aaagtctcta aaatatcaca gatttaccta 1560
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gagggcaaca tttagataca ggaaaatttt acatagtgtt ttgtcttagg attagacgtg 1620
accagattga tcctgtttga ttttggagag atcctattct aacaaatact ctaaaatgat 1680
aaaattgagg tacaactctc ttaaaagagt atggataact atattttctg gattctggag 1740
gttgataacc atatgcactt aacattatat tctataaaca ttaagtagtg ccagttatga 1800
gattcccagt tcttactaaa ttgtattagc aggagctggt aattacttgt attatcacat 1860
gtaactaata atttgaacta tacttgaagg accgtgttga tgtcaggtat ttacagtggt 1920
tggaagatag cagtattatt agcataagct gcatacgtaa tattcagtaa ctgccatatt 1980
atataacaaa tttacattca caaattcagt atcctgttaa gtgtcatatt cttgtaatct 2040
gcattctcca ggagttttat gtgtttaata gatgaattta ttttatttct aaaggtattc 2100
aaatgtttca gcaccatata atagaaatac ccaattatat tctagttcct ttatgtcctg 2160
tacatcattc tctgcttgga tttccattat tctgtttggt tagagaataa aattggtaat 2220
tgcatttg 2228

<210> 212
<211> 471
<212> PRT
<213> Homo sapiens

<400> 212
Met Ala Arg Glu Met Thr Ile Leu Gly Ser Ala Val Leu Thr Leu Leu
1 5 10 15
Leu Ala Gly Tyr Leu Ala Gln Gln Tyr Leu Pro Leu Pro Thr Pro Lys
20 25 30
Val Ile Gly Ile Asp Leu Gly Thr Thr Tyr Cys Ser Val Gly Val Phe
35 40 45
Phe Pro Gly Thr Gly Lys Val Lys Val Ile Pro Asp Glu Asn Gly His
50 55 60
Ile Ser Ile Pro Ser Met Val Ser Phe Thr Asp Asn Asp Val Tyr Val
65 70 75 80
Gly Tyr Glu Ser Val Glu Leu Ala Asp Ser Asn Pro Gln Asn Thr Ile
85 90 95
Tyr Asp Ala Lys Arg Phe Ile Gly Lys Ile Phe Thr Ala Glu Glu Leu
100 105 110
Glu Ala Glu Ile Gly Arg Tyr Pro Phe Lys Val Leu Asn Lys Asn Gly
115 120 125
Met Val Glu Phe Ser Val Thr Ser Asn Glu Thr Ile Thr Val Ser Pro
130 135 140
Glu Tyr Val Gly Ser Arg Leu Leu Leu Lys Leu Lys Glu Met Ala Glu
145 150 155 160
Ala Tyr Leu Gly Met Pro Val Ala Asn Ala Val Ile Ser Val Pro Ala
165 170 175
Glu Phe Asp Leu Lys Gln Arg Asn Ser Thr Ile Glu Ala Ala Asn Leu
180 185 190
Ala Gly Leu Lys Ile Leu Arg Val Ile Asn Glu Pro Thr Ala Ala Ala
195 200 205
Met Ala Tyr Gly Leu His Lys Ala Asp Val Phe His Val Leu Val Ile
210 215 220
Asp Leu Gly Gly Gly Thr Leu Asp Val Ser Leu Leu Asn Lys Gln Gly
225 230 235 240
Gly Met Phe Leu Thr Arg Ala Met Ser Gly Asn Asn Lys Leu Gly Gly
245 250 255
Gln Asp Phe Asn Gln Arg Leu Leu Gln Tyr Leu Tyr Lys Gln Ile Tyr
260 265 270
Gln Thr Tyr Gly Phe Val Pro Ser Arg Lys Glu Glu Ile His Arg Leu
275 280 285
Arg Gln Ala Val Glu Met Val Lys Leu Asn Leu Thr Leu His Gln Ser
290 295 300
Ala Gln Leu Ser Val Leu Leu Thr Val Glu Glu Gln Asp Arg Lys Glu
305 310 315 320

```
Pro His Ser Ser Asp Thr Glu Leu Pro Lys Asp Lys Leu Ser Ser Ala
                325                 330                 335
Asp Asp His Arg Val Asn Ser Gly Phe Gly Arg Gly Leu Ser Asp Lys
            340                 345                 350
Lys Ser Gly Glu Ser Gln Val Leu Phe Glu Thr Glu Ile Ser Arg Lys
        355                 360                 365
Leu Phe Asp Thr Leu Asn Glu Asp Leu Phe Gln Lys Ile Leu Val Pro
    370                 375                 380
Ile Gln Gln Val Leu Lys Glu Gly His Leu Glu Lys Thr Glu Ile Asp
385                 390                 395                 400
Glu Val Val Leu Val Gly Gly Ser Thr Arg Ile Pro Arg Ile Arg Gln
                405                 410                 415
Val Ile Gln Glu Phe Phe Gly Lys Asp Pro Asn Thr Ser Val Asp Pro
            420                 425                 430
Asp Leu Ala Val Val Thr Gly Val Ala Ile Gln Ala Gly Ile Asp Gly
        435                 440                 445
Gly Ser Trp Pro Leu Gln Val Ser Ala Leu Glu Ile Pro Asn Lys His
    450                 455                 460
Leu Gln Lys Thr Asn Phe Asn
465                 470
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<210> 213
<211> 1224
<212> DNA
<213> Homo sapiens

<400> 213

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ggccgggaga gtagcagtgc cttggacccc agctctcctc cccctttctc tctaaggatg 60
gcccagaagg agaactccta cccctggccc tacggccgac agacggctcc atctggcctg 120
agcaccctgc cccagcgagt cctccggaaa gagcctgtca ccccatctgc acttgtcctc 180
atgagccgct ccaatgtcca gcccacagct gcccctggcc agaaggtgat ggagaatagc 240
agtgggacac ccgacatctt aacgcggcac ttcacaattg atgactttga gattgggcgt 300
cctctgggca aaggcaagtt tggaaacgtg tacttggctc gggagaagaa aagccatttc 360
atcgtggcgc tcaaggtcct cttcaagtcc cagatagaga aggagggcgt ggagcatcag 420
ctgcgcagag agatcgaaat ccaggcccac ctgcaccatc ccaacatcct gcgtctctac 480
aactattttt atgaccggag gaggatctac ttgattctag agtatgcccc ccgcggggag 540
ctctacaagg agctgcagaa gagctgcaca tttgacgagc agcgaacagc cacgatcatg 600
gaggagttgg cagatgctct aatgtactgc catgggaaga aggtgattca cagagacata 660
aagccagaaa atctgctctt agggctcaag ggagagctga agattgctga cttcggctgg 720
tctgtgcatg cgccctccct gaggaggaag acaatgtgtg gcaccctgga ctacctgccc 780
ccagagatga ttgaggggcg catgcacaat gagaaggtgg atctgtggtg cattggagtg 840
ctttgctatg agctgctggt ggggaaccca ccctttgaga gtgcatcaca caacgagacc 900
tatcgccgca tcgtcaaggt ggacctaaag ttccccgctt ctgtgcccac gggagcccag 960
gacctcatct ccaaactgct caggcataac ccctcggaac ggctgcccct ggcccaggtc 1020
tcagcccacc cttgggtccg ggccaactct cggagggtgc tgcctccctc tgcccttcaa 1080
tctgtcgcct gatggtccct gtcattcact cgggtgcgtg tgtttgtatg tctgtgtatg 1140
tatagggg aa agaagggatc cctaactgtt cccttatctg ttttctacct cctcctttgt 1200
ttaataaagg ctgaagcttt ttgt                                          1224
```

<210> 214
<211> 344
<212> PRT
<213> Homo sapiens

<400> 214

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Met Ala Gln Lys Glu Asn Ser Tyr Pro Trp Pro Tyr Gly Arg Gln Thr
 1               5                  10                  15
Ala Pro Ser Gly Leu Ser Thr Leu Pro Gln Arg Val Leu Arg Lys Glu
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```
                20                  25                  30
Pro Val Thr Pro Ser Ala Leu Val Leu Met Ser Arg Ser Asn Val Gln
        35                  40                  45
Pro Thr Ala Ala Pro Gly Gln Lys Val Met Glu Asn Ser Ser Gly Thr
    50                  55                  60
Pro Asp Ile Leu Thr Arg His Phe Thr Ile Asp Asp Phe Glu Ile Gly
65                  70                  75                  80
Arg Pro Leu Gly Lys Gly Lys Phe Gly Asn Val Tyr Leu Ala Arg Glu
                85                  90                  95
Lys Lys Ser His Phe Ile Val Ala Leu Lys Val Leu Phe Lys Ser Gln
            100                 105                 110
Ile Glu Lys Glu Gly Val Glu His Gln Leu Arg Arg Glu Ile Glu Ile
        115                 120                 125
Gln Ala His Leu His His Pro Asn Ile Leu Arg Leu Tyr Asn Tyr Phe
    130                 135                 140
Tyr Asp Arg Arg Arg Ile Tyr Leu Ile Leu Glu Tyr Ala Pro Arg Gly
145                 150                 155                 160
Glu Leu Tyr Lys Glu Leu Gln Lys Ser Cys Thr Phe Asp Glu Gln Arg
                165                 170                 175
Thr Ala Thr Ile Met Glu Glu Leu Ala Asp Ala Leu Met Tyr Cys His
            180                 185                 190
Gly Lys Lys Val Ile His Arg Asp Ile Lys Pro Glu Asn Leu Leu Leu
        195                 200                 205
Gly Leu Lys Gly Glu Leu Lys Ile Ala Asp Phe Gly Trp Ser Val His
    210                 215                 220
Ala Pro Ser Leu Arg Arg Lys Thr Met Cys Gly Thr Leu Asp Tyr Leu
225                 230                 235                 240
Pro Pro Glu Met Ile Glu Gly Arg Met His Asn Glu Lys Val Asp Leu
                245                 250                 255
Trp Cys Ile Gly Val Leu Cys Tyr Glu Leu Leu Val Gly Asn Pro Pro
            260                 265                 270
Phe Glu Ser Ala Ser His Asn Glu Thr Tyr Arg Arg Ile Val Lys Val
        275                 280                 285
Asp Leu Lys Phe Pro Ala Ser Val Pro Thr Gly Ala Gln Asp Leu Ile
    290                 295                 300
Ser Lys Leu Leu Arg His Asn Pro Ser Glu Arg Leu Pro Leu Ala Gln
305                 310                 315                 320
Val Ser Ala His Pro Trp Val Arg Ala Asn Ser Arg Arg Val Leu Pro
                325                 330                 335
Pro Ser Ala Leu Gln Ser Val Ala
            340
```

<210> 215
<211> 1421
<212> DNA
<213> Homo sapiens

<400> 215

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acttactgcg ggacggcctt ggagagtact cgggttcgtg aacttcccgg aggcgcaatg 60
agctgcatta acctgcccac tgtgctgccc ggctccccca gcaagacccg ggggcagatc 120
caggtgattc tcgggccgat gttctcagga aaaagcacag agttgatgag acgcgtccgt 180
cgcttccaga ttgctcagta caagtgcctg gtgatcaagt atgccaaaga cactcgctac 240
agcagcagct tctgcacaca tgaccggaac accatggagg cgctgcccgc ctgcctgctc 300
cgagacgtgg cccaggaggc cctgggcgtg gctgtcatag gcatcgacga ggggcagttt 360
ttccctgaca tcatggagtt ctgcgaggcc atggccaacg ccgggaagac cgtaattgtg 420
gctgcactgg atgggacctt ccagaggaag ccatttgggg ccatcctgaa cctggtgccg 480
ctggccgaga gcgtggtgaa gctgacggcg gtgtgcatgg agtgcttccg ggaagccgcc 540
tataccaaga ggctcggcac agagaaggag gtcgaggtga ttgggggagc agacaagtac 600
```

cactccgtgt gtcggctctg ctacttcaag aaggcctcag gccagcctgc cgggccggac 660
aacaaagaga actgcccagt gccaggaaag ccaggggaag ccgtggctgc caggaagctc 720
tttgccccac agcagattct gcaatgcagc cctgccaact gagggacctg caagggccgc 780
ccgctccctt cctgccactg ccgcctactg gacgctgccc tgcatgctgc ccagccactc 840
caggaggaag tcgggaggcg tggagggtga ccacaccttg gccttctggg aactctcctt 900
tgtgtggctg ccccacctgc cgcatgctcc ctcctctcct acccactggt ctgcttaaag 960
cttccctctc agctgctggg acgatcgccc aggctggagc tggccccgct tggtggcctg 1020
ggatctggca cactccctct ccttggggtg agggacagag ccccacgctg ttgacatcag 1080
cctgcttctt cccctctgcg gctttcactg ctgagtttct gttctccctg ggaagcctgt 1140
gccagcacct ttgagccttg gcccacactg aggcttaggc ctctctgcct gggatgggct 1200
cccaccctcc cctgaggatg gcctggattc acgccctctt gtttcctttt gggctcaaag 1260
cccttcctac ctctggtgat ggtttccaca ggaacaacag catctttcac caagatgggt 1320
ggcaccaacc ttgctgggac ttggatccca ggggcttatc tcttcaagtg tggagagggc 1380
agggtccacg cctctgctgt agcttatgaa attaactaat t 1421

<210> 216
<211> 234
<212> PRT
<213> Homo sapiens

<400> 216
Met Ser Cys Ile Asn Leu Pro Thr Val Leu Pro Gly Ser Pro Ser Lys
1 5 10 15
Thr Arg Gly Gln Ile Gln Val Ile Leu Gly Pro Met Phe Ser Gly Lys
20 25 30
Ser Thr Glu Leu Met Arg Arg Val Arg Arg Phe Gln Ile Ala Gln Tyr
35 40 45
Lys Cys Leu Val Ile Lys Tyr Ala Lys Asp Thr Arg Tyr Ser Ser Ser
50 55 60
Phe Cys Thr His Asp Arg Asn Thr Met Glu Ala Leu Pro Ala Cys Leu
65 70 75 80
Leu Arg Asp Val Ala Gln Glu Ala Leu Gly Val Ala Val Ile Gly Ile
85 90 95
Asp Glu Gly Gln Phe Phe Pro Asp Ile Met Glu Phe Cys Glu Ala Met
100 105 110
Ala Asn Ala Gly Lys Thr Val Ile Val Ala Ala Leu Asp Gly Thr Phe
115 120 125
Gln Arg Lys Pro Phe Gly Ala Ile Leu Asn Leu Val Pro Leu Ala Glu
130 135 140
Ser Val Val Lys Leu Thr Ala Val Cys Met Glu Cys Phe Arg Glu Ala
145 150 155 160
Ala Tyr Thr Lys Arg Leu Gly Thr Glu Lys Glu Val Glu Val Ile Gly
165 170 175
Gly Ala Asp Lys Tyr His Ser Val Cys Arg Leu Cys Tyr Phe Lys Lys
180 185 190
Ala Ser Gly Gln Pro Ala Gly Pro Asp Asn Lys Glu Asn Cys Pro Val
195 200 205
Pro Gly Lys Pro Gly Glu Ala Val Ala Ala Arg Lys Leu Phe Ala Pro
210 215 220
Gln Gln Ile Leu Gln Cys Ser Pro Ala Asn
225 230

<210> 217
<211> 2307
<212> DNA
<213> Homo sapiens

<220>

<221> misc_feature
<222> 1691, 1698, 1705, 1708, 1709, 1713, 1717, 1720, 1724, 1728, 1733, 1741, 1746, 1748, 1755, 1770, 1774, 1791, 1802, 1821, 1838, 1856, 1859, 1864, 1908, 1959, 1997, 2012, 2038, 2143
<223> n = A,T,C or G

<400> 217
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agtcgacccc gcgtccggtt ttaatcaagc tgcccaaagt cccccaatca ctcctggaat 60
acacagagag aggcagcagc ttgctcagcg gacaaggatg ctgggcgtga gggaccaagg 120
cctgccctgc actcgggcct cctccagcca gtgctgacca gggacttctg acctgctggc 180
cagccaggac ctgtgtgggg aggccctcct gctgccttgg ggtgacaatc tcagctccag 240
gctacaggga gaccgggagg atcacagagc cagcatgtta caggatcctg acagtgatca 300
acctctgaac agcctcgatg tcaaacccct gcgcaaaccc cgtatcccca tggagacctt 360
cagaaaggtg ggatccccca tcatcatagc actactgagc ctggcgagta tcatcattgt 420
ggttgtcctc atcaaggtga ttctggataa atactacttc ctctgcgggc agcctctcca 480
cttcatcccg aggaagcagc tgtgtgacgg agagctggac tgtcccttgg gggaggacga 540
ggagcactgt gtcaagagct tccccgaagg gcctgcagtg gcagtccgcc tctccaagga 600
ccgatccaca ctgcaggtgc tggactcggc cacagggaac tggttctctg cctgtttcga 660
caacttcaca gaagctctcg ctgagacagc ctgtaggcag atgggctaca gcagcaaacc 720
cactttcaga gctgtggaga ttggcccaga ccaggatctg gatgttgttg aaatcacaga 780
aaacagccag gagcttcgca tgcggaactc aagtgggccc tgtctctcag gctccctggt 840
ctccctgcac tgtcttgcct gtgggaagag cctgaagacc ccccgtgtgg tgggtgggga 900
ggaggcctct gtggattctt ggccttggca ggtcagcatc cagtacgaca aacagcacgt 960
ctgtggaggg agcatcctgg acccccactg ggtcctcacg gcagcccact gcttcaggaa 1020
acataccgat gtgttcaact ggaaggtgcg ggcaggctca gacaaactgg gcagcttccc 1080
atccctggct gtggccaaga tcatcatcat tgaattcaac cccatgtacc ccaaagacaa 1140
tgacatcgcc ctcatgaagc tgcagttccc actcactttc tcaggcacag tcaggcccat 1200
ctgtctgccc ttctttgatg aggagctcac tccagccacc ccactctgga tcattggatg 1260
gggctttacg aagcagaatg gagggaagat gtctgacata ctgctgcagg cgtcagtcca 1320
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ctgcgggggc ccgagcaccc caggagtata caccaaggtc tcagcctatc tcaactggat 1560
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ttccttcctg ccctgcccac ctggggatcc ccccaaagtca gacacagagc aagagtcccc 1680
ttgggtacac nccctctngc ccacnagnnc ctncagncan tttncttngg agncagcaaa 1740
ngggcncntc aattncctgt aagagacccn tcgncagccc agaggcgccc nagaggaagt 1800
cnagcagccc tagctcggcc nacacttggt gctcccangc atcccaggga gagacnacna 1860
gccncactga acaaggtctc aggggtattg ctaagccaag aaggaacntt tcccacacta 1920
ctgaatggaa gcaggctgtc ttgtaaaagc ccagatcanc tgtgggctgg agaggagaag 1980
gaaagggtct gcgccangcc ctgtccgtct tncacccatc cccaagccta ctagagcnaa 2040
gaaaccagtt gtaatataaa atgcactgcc ctactgttgg tatgactacc gttacctact 2100
gttgtcattg ttattacagc tatggccact attattaaag agnctgtgta acatcaaaaa 2160
aaaaaaaaaa aaaaaaaaaa araaaaaaaa ataaataaaa aaaaactcga gggggggccc 2220
ggtacccaat tcgccctata gtgagtcgta ttacaattca ctggccgtcg ttttacaacg 2280
tcgtgactgg gaaaaccctg gcgttac 2307
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<210> 218
<211> 428
<212> PRT
<213> Homo sapiens

<400> 218
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Met Leu Gln Asp Pro Asp Ser Asp Gln Pro Leu Asn Ser Leu Asp Val
 1               5                  10                  15
Lys Pro Leu Arg Lys Pro Arg Ile Pro Met Glu Thr Phe Arg Lys Val
            20                  25                  30
Gly Ile Pro Ile Ile Ile Ala Leu Leu Ser Leu Ala Ser Ile Ile Ile
        35                  40                  45
```

```
Val Val Val Leu Ile Lys Val Ile Leu Asp Lys Tyr Tyr Phe Leu Cys
    50                  55                  60
Gly Gln Pro Leu His Phe Ile Pro Arg Lys Gln Leu Cys Asp Gly Glu
65                  70                  75                  80
Leu Asp Cys Pro Leu Gly Glu Asp Glu Glu His Cys Val Lys Ser Phe
                85                  90                  95
Pro Glu Gly Pro Ala Val Ala Val Arg Leu Ser Lys Asp Arg Ser Thr
            100                 105                 110
Leu Gln Val Leu Asp Ser Ala Thr Gly Asn Trp Phe Ser Ala Cys Phe
        115                 120                 125
Asp Asn Phe Thr Glu Ala Leu Ala Glu Thr Ala Cys Arg Gln Met Gly
    130                 135                 140
Tyr Ser Ser Lys Pro Thr Phe Arg Ala Val Glu Ile Gly Pro Asp Gln
145                 150                 155                 160
Asp Leu Asp Val Val Glu Ile Thr Glu Asn Ser Gln Glu Leu Arg Met
                165                 170                 175
Arg Asn Ser Ser Gly Pro Cys Leu Ser Gly Ser Leu Val Ser Leu His
            180                 185                 190
Cys Leu Ala Cys Gly Lys Ser Leu Lys Thr Pro Arg Val Val Gly Gly
        195                 200                 205
Glu Glu Ala Ser Val Asp Ser Trp Pro Trp Gln Val Ser Ile Gln Tyr
    210                 215                 220
Asp Lys Gln His Val Cys Gly Gly Ser Ile Leu Asp Pro His Trp Val
225                 230                 235                 240
Leu Thr Ala Ala His Cys Phe Arg Lys His Thr Asp Val Phe Asn Trp
                245                 250                 255
Lys Val Arg Ala Gly Ser Asp Lys Leu Gly Ser Phe Pro Ser Leu Ala
            260                 265                 270
Val Ala Lys Ile Ile Ile Ile Glu Phe Asn Pro Met Tyr Pro Lys Asp
        275                 280                 285
Asn Asp Ile Ala Leu Met Lys Leu Gln Phe Pro Leu Thr Phe Ser Gly
    290                 295                 300
Thr Val Arg Pro Ile Cys Leu Pro Phe Phe Asp Glu Glu Leu Thr Pro
305                 310                 315                 320
Ala Thr Pro Leu Trp Ile Ile Gly Trp Gly Phe Thr Lys Gln Asn Gly
                325                 330                 335
Gly Lys Met Ser Asp Ile Leu Leu Gln Ala Ser Val Gln Val Ile Asp
            340                 345                 350
Ser Thr Arg Cys Asn Ala Asp Asp Ala Tyr Gln Gly Glu Val Thr Glu
        355                 360                 365
Lys Met Met Cys Ala Gly Ile Pro Glu Gly Gly Val Asp Thr Cys Gln
    370                 375                 380
Gly Asp Ser Gly Gly Pro Leu Met Tyr Gln Ser Asp Gln Trp His Val
385                 390                 395                 400
Val Gly Ile Val Ser Trp Gly Tyr Gly Cys Gly Gly Pro Ser Thr Pro
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Gly Val Tyr Thr Lys Val Ser Ala Tyr Leu Asn Trp
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<210> 219
<211> 556
<212> DNA
<213> Homo sapiens

<400> 219

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agtcgaaact gaagaagaca gagacgcaag agaaaaatcc actgccttcc aaagaaacga 180
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ttgaacagga gaagcaagca ggcgaatcgt aatgaggcgt gcgccgccaa tatgcactgt 240
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caaagaggtt ggatcaagtt taaatgactg tgctgcccct ttcacatcaa agaactactg 360
acaacgaagg ccgcgctgcc tttcccatct gtctatctat ctggctggca gggaaggaaa 420
gaacttgcat gttggtgaag gaagaagtgg ggtggaagaa gtggggtggg acgacagtga 480
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agtgccattt tttttt                                                 556
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<210> 220
<211> 44
<212> PRT
<213> Homo sapiens

<400> 220

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Met Ser Asp Lys Pro Asp Met Ala Glu Ile Glu Lys Phe Asp Lys Ser
 1               5                  10                  15
Lys Leu Lys Lys Thr Glu Thr Gln Glu Lys Asn Pro Leu Pro Ser Lys
            20                  25                  30
Glu Thr Ile Glu Gln Glu Lys Gln Ala Gly Glu Ser
        35                  40
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<210> 221
<211> 4792
<212> DNA
<213> Homo sapiens

<400> 221

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tctgttgaaa gaatctatca aaagaaaaca caattggaac atattttgct ccgcccagac 180
acctacattg gttctgtgga attagtgacc cagcaaatgt gggtttacga tgaagatgtt 240
ggcattaact atagggaagt cacttttgtt cctggtttgt acaaaatctt tgatgagatt 300
ctagttaatg ctgcggacaa caaacaaagg gacccaaaaa tgtcttgtat tagagtcaca 360
attgatccgg aaaacaattt aattagtata tggaataatg gaaaaggtat tcctgttgtt 420
gaacacaaag ttgaaaagat gtatgtccca gctctcatat ttggacagct cctaacttct 480
agtaactatg atgatgatga aaagaaagtg acaggtggtc gaaatggcta tggagccaaa 540
ttgtgtaaca tattcagtac caaatttact gtggaaacag ccagtagaga atacaagaaa 600
atgttcaaac agacatggat ggataatatg ggaagagctg gtgagatgga actcaagccc 660
ttcaatggag aagattatac atgtatcacc tttcagcctg atttgtctaa gtttaaaatg 720
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tccaccaaag atgtcaaagt ctttcttaat ggaaataaac tgccagtaaa aggatttcgt 840
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gtagctgatc agattgtgac taaacttgtt gatgttgtga agaagaagaa caagggtggt 1080
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aaagtcaaat attacaaagg tttgggcacc agcacatcaa aggaagctaa agaatacttt 1920
gcagatatga aaagacatcg tatccagttc aaatattctg gtcctgaaga tgatgctgct 1980
atcagcctgg cctttagcaa aaaacagata gatgatcgaa aggaatggtt aactaatttc 2040
atggaggata gaagacaacg aaagttactt gggcttcctg aggattactt gtatggacaa 2100
actaccacat atctgacata taatgacttc atcaacaagg aacttatctt gttctcaaat 2160
tctgataacg agagatctat cccttctatg gtggatggtt tgaaaccagg tcagagaaag 2220
gttttgttta cttgcttcaa acggaatgac aagcgagaag taaaggttgc ccaattagct 2280
ggatcagtgg ctgaaatgtc ttcttatcat catggtgaga tgtcactaat gatgaccatt 2340
atcaatttgg ctcagaattt tgtgggtagc aataatctaa acctcttgca gcccattggt 2400
cagtttggta ccaggctaca tggtggcaag gattctgcta gtccacgata catctttaca 2460
atgctcagct ctttggctcg attgttattt ccaccaaaag atgatcacac gttgaagttt 2520
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caagaagatg gtgtggaact agaaggccta aaacaaagat tagaaaagaa acagaaaaga 3840
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gatttggatt cagatgaaga tttctcagat tttgatgaaa aaactgatga tgaagatttt 4080
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gttttaaagt tacctgaagc tcttaacttc ctcccctctg aatttagttt ggggaaggtg 4740
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<210> 222
<211> 1531
<212> PRT
<213> Homo sapiens

<400> 222
Met Glu Val Ser Pro Leu Gln Pro Val Asn Glu Asn Met Gln Val Asn
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Lys Ile Lys Lys Asn Glu Asp Ala Lys Lys Arg Leu Ser Val Glu Arg

20 25 30
Ile Tyr Gln Lys Lys Thr Gln Leu Glu His Ile Leu Leu Arg Pro Asp
35 40 45
Thr Tyr Ile Gly Ser Val Glu Leu Val Thr Gln Gln Met Trp Val Tyr
50 55 60
Asp Glu Asp Val Gly Ile Asn Tyr Arg Glu Val Thr Phe Val Pro Gly
65 70 75 80
Leu Tyr Lys Ile Phe Asp Glu Ile Leu Val Asn Ala Ala Asp Asn Lys
85 90 95
Gln Arg Asp Pro Lys Met Ser Cys Ile Arg Val Thr Ile Asp Pro Glu
100 105 110
Asn Asn Leu Ile Ser Ile Trp Asn Asn Gly Lys Gly Ile Pro Val Val
115 120 125
Glu His Lys Val Glu Lys Met Tyr Val Pro Ala Leu Ile Phe Gly Gln
130 135 140
Leu Leu Thr Ser Ser Asn Tyr Asp Asp Asp Glu Lys Lys Val Thr Gly
145 150 155 160
Gly Arg Asn Gly Tyr Gly Ala Lys Leu Cys Asn Ile Phe Ser Thr Lys
165 170 175
Phe Thr Val Glu Thr Ala Ser Arg Glu Tyr Lys Lys Met Phe Lys Gln
180 185 190
Thr Trp Met Asp Asn Met Gly Arg Ala Gly Glu Met Glu Leu Lys Pro
195 200 205
Phe Asn Gly Glu Asp Tyr Thr Cys Ile Thr Phe Gln Pro Asp Leu Ser
210 215 220
Lys Phe Lys Met Gln Ser Leu Asp Lys Asp Ile Val Ala Leu Met Val
225 230 235 240
Arg Arg Ala Tyr Asp Ile Ala Gly Ser Thr Lys Asp Val Lys Val Phe
245 250 255
Leu Asn Gly Asn Lys Leu Pro Val Lys Gly Phe Arg Ser Tyr Val Asp
260 265 270
Met Tyr Leu Lys Asp Lys Leu Asp Glu Thr Gly Asn Ser Leu Lys Val
275 280 285
Ile His Glu Gln Val Asn His Arg Trp Glu Val Cys Leu Thr Met Ser
290 295 300
Glu Lys Gly Phe Gln Gln Ile Ser Phe Val Asn Ser Ile Ala Thr Ser
305 310 315 320
Lys Gly Gly Arg His Val Asp Tyr Val Ala Asp Gln Ile Val Thr Lys
325 330 335
Leu Val Asp Val Val Lys Lys Lys Asn Lys Gly Gly Val Ala Val Lys
340 345 350
Ala His Gln Val Lys Asn His Met Trp Ile Phe Val Asn Ala Leu Ile
355 360 365
Glu Asn Pro Thr Phe Asp Ser Gln Thr Lys Glu Asn Met Thr Leu Gln
370 375 380
Pro Lys Ser Phe Gly Ser Thr Cys Gln Leu Ser Glu Lys Phe Ile Lys
385 390 395 400
Ala Ala Ile Gly Cys Gly Ile Val Glu Ser Ile Leu Asn Trp Val Lys
405 410 415
Phe Lys Ala Gln Val Gln Leu Asn Lys Lys Cys Ser Ala Val Lys His
420 425 430
Asn Arg Ile Lys Gly Ile Pro Lys Leu Asp Asp Ala Asn Asp Ala Gly
435 440 445
Gly Arg Asn Ser Thr Glu Cys Thr Leu Ile Leu Thr Glu Gly Asp Ser
450 455 460
Ala Lys Thr Leu Ala Val Ser Gly Leu Gly Val Val Gly Arg Asp Lys
465 470 475 480
Tyr Gly Val Phe Pro Leu Arg Gly Lys Ile Leu Asn Val Arg Glu Ala
485 490 495

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Ser His Lys Gln Ile Met Glu Asn Ala Glu Ile Asn Asn Ile Ile Lys
            500                 505                 510
Ile Val Gly Leu Gln Tyr Lys Lys Asn Tyr Glu Asp Glu Asp Ser Leu
        515                 520                 525
Lys Thr Leu Arg Tyr Gly Lys Ile Met Ile Met Thr Asp Gln Asp Gln
    530                 535                 540
Asp Gly Ser His Ile Lys Gly Leu Leu Ile Asn Phe Ile His His Asn
545                 550                 555                 560
Trp Pro Ser Leu Leu Arg His Arg Phe Leu Glu Glu Phe Ile Thr Pro
                565                 570                 575
Ile Val Lys Val Ser Lys Asn Lys Gln Glu Met Ala Phe Tyr Ser Leu
            580                 585                 590
Pro Glu Phe Glu Glu Trp Lys Ser Ser Thr Pro Asn His Lys Lys Trp
        595                 600                 605
Lys Val Lys Tyr Tyr Lys Gly Leu Gly Thr Ser Thr Ser Lys Glu Ala
    610                 615                 620
Lys Glu Tyr Phe Ala Asp Met Lys Arg His Arg Ile Gln Phe Lys Tyr
625                 630                 635                 640
Ser Gly Pro Glu Asp Asp Ala Ala Ile Ser Leu Ala Phe Ser Lys Lys
                645                 650                 655
Gln Ile Asp Asp Arg Lys Glu Trp Leu Thr Asn Phe Met Glu Asp Arg
            660                 665                 670
Arg Gln Arg Lys Leu Leu Gly Leu Pro Glu Asp Tyr Leu Tyr Gly Gln
        675                 680                 685
Thr Thr Thr Tyr Leu Thr Tyr Asn Asp Phe Ile Asn Lys Glu Leu Ile
    690                 695                 700
Leu Phe Ser Asn Ser Asp Asn Glu Arg Ser Ile Pro Ser Met Val Asp
705                 710                 715                 720
Gly Leu Lys Pro Gly Gln Arg Lys Val Leu Phe Thr Cys Phe Lys Arg
                725                 730                 735
Asn Asp Lys Arg Glu Val Lys Val Ala Gln Leu Ala Gly Ser Val Ala
            740                 745                 750
Glu Met Ser Ser Tyr His His Gly Glu Met Ser Leu Met Met Thr Ile
        755                 760                 765
Ile Asn Leu Ala Gln Asn Phe Val Gly Ser Asn Asn Leu Asn Leu Leu
    770                 775                 780
Gln Pro Ile Gly Gln Phe Gly Thr Arg Leu His Gly Gly Lys Asp Ser
785                 790                 795                 800
Ala Ser Pro Arg Tyr Ile Phe Thr Met Leu Ser Ser Leu Ala Arg Leu
                805                 810                 815
Leu Phe Pro Pro Lys Asp Asp His Thr Leu Lys Phe Leu Tyr Asp Asp
            820                 825                 830
Asn Gln Arg Val Glu Pro Glu Trp Tyr Ile Pro Ile Ile Pro Met Val
        835                 840                 845
Leu Ile Asn Gly Ala Glu Gly Ile Gly Thr Gly Trp Ser Cys Lys Ile
    850                 855                 860
Pro Asn Phe Asp Val Arg Glu Ile Val Asn Asn Ile Arg Arg Leu Met
865                 870                 875                 880
Asp Gly Glu Glu Pro Leu Pro Met Leu Pro Ser Tyr Lys Asn Phe Lys
                885                 890                 895
Gly Thr Ile Glu Glu Leu Ala Pro Asn Gln Tyr Val Ile Ser Gly Glu
            900                 905                 910
Val Ala Ile Leu Asn Ser Thr Thr Ile Glu Ile Ser Glu Leu Pro Val
        915                 920                 925
Arg Thr Trp Thr Gln Thr Tyr Lys Glu Gln Val Leu Glu Pro Met Leu
    930                 935                 940
Asn Gly Thr Glu Lys Thr Pro Pro Leu Ile Thr Asp Tyr Arg Glu Tyr
945                 950                 955                 960
His Thr Asp Thr Thr Val Lys Phe Val Val Lys Met Thr Glu Glu Lys
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                965                 970                 975
Leu Ala Glu Ala Glu Arg Val Gly Leu His Lys Val Phe Lys Leu Gln
            980                 985                 990
Thr Ser Leu Thr Cys Asn Ser Met Val Leu Phe Asp His Val Gly Cys
        995                 1000                1005
Leu Lys Lys Tyr Asp Thr Val Leu Asp Ile Leu Arg Asp Phe Phe Glu
    1010                1015                1020
Leu Arg Leu Lys Tyr Tyr Gly Leu Arg Lys Glu Trp Leu Leu Gly Met
1025                1030                1035                1040
Leu Gly Ala Glu Ser Ala Lys Leu Asn Asn Gln Ala Arg Phe Ile Leu
                1045                1050                1055
Glu Lys Ile Asp Gly Lys Ile Ile Ile Glu Asn Lys Pro Lys Lys Glu
            1060                1065                1070
Leu Ile Lys Val Leu Ile Gln Arg Gly Tyr Asp Ser Asp Pro Val Lys
        1075                1080                1085
Ala Trp Lys Glu Ala Gln Gln Lys Val Pro Asp Glu Glu Glu Asn Glu
    1090                1095                1100
Glu Ser Asp Asn Glu Lys Glu Thr Glu Lys Ser Asp Ser Val Thr Asp
1105                1110                1115                1120
Ser Gly Pro Thr Phe Asn Tyr Leu Leu Asp Met Pro Leu Trp Tyr Leu
                1125                1130                1135
Thr Lys Glu Lys Lys Asp Glu Leu Cys Arg Leu Arg Asn Glu Lys Glu
            1140                1145                1150
Gln Glu Leu Asp Thr Leu Lys Arg Lys Ser Pro Ser Asp Leu Trp Lys
        1155                1160                1165
Glu Asp Leu Ala Thr Phe Ile Glu Glu Leu Glu Ala Val Glu Ala Lys
    1170                1175                1180
Glu Lys Gln Asp Glu Gln Val Gly Leu Pro Gly Lys Gly Gly Lys Ala
1185                1190                1195                1200
Lys Gly Lys Lys Thr Gln Met Ala Glu Val Leu Pro Ser Pro Arg Gly
                1205                1210                1215
Gln Arg Val Ile Pro Arg Ile Thr Ile Glu Met Lys Ala Glu Ala Glu
            1220                1225                1230
Lys Lys Asn Lys Lys Lys Ile Lys Asn Glu Asn Thr Glu Gly Ser Pro
        1235                1240                1245
Gln Glu Asp Gly Val Glu Leu Glu Gly Leu Lys Gln Arg Leu Glu Lys
    1250                1255                1260
Lys Gln Lys Arg Glu Pro Gly Thr Lys Thr Lys Lys Gln Thr Thr Leu
1265                1270                1275                1280
Ala Phe Lys Pro Ile Lys Lys Gly Lys Lys Arg Asn Pro Trp Pro Asp
                1285                1290                1295
Ser Glu Ser Asp Arg Ser Ser Asp Glu Ser Asn Phe Asp Val Pro Pro
            1300                1305                1310
Arg Glu Thr Glu Pro Arg Arg Ala Ala Thr Lys Thr Lys Phe Thr Met
        1315                1320                1325
Asp Leu Asp Ser Asp Glu Asp Phe Ser Asp Phe Asp Glu Lys Thr Asp
    1330                1335                1340
Asp Glu Asp Phe Val Pro Ser Asp Ala Ser Pro Pro Lys Thr Lys Thr
1345                1350                1355                1360
Ser Pro Lys Leu Ser Asn Lys Glu Leu Lys Pro Gln Lys Ser Val Val
                1365                1370                1375
Ser Asp Leu Glu Ala Asp Asp Val Lys Gly Ser Val Pro Leu Ser Ser
            1380                1385                1390
Ser Pro Pro Ala Thr His Phe Pro Asp Glu Thr Glu Ile Thr Asn Pro
        1395                1400                1405
Val Pro Lys Lys Asn Val Thr Val Lys Lys Thr Ala Ala Lys Ser Gln
    1410                1415                1420
Ser Ser Thr Ser Thr Thr Gly Ala Lys Lys Arg Ala Ala Pro Lys Gly
1425                1430                1435                1440
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Thr Lys Arg Asp Pro Ala Leu Asn Ser Gly Val Ser Gln Lys Pro Asp
1445 1450 1455
Pro Ala Lys Thr Lys Asn Arg Arg Lys Arg Lys Pro Ser Thr Ser Asp
1460 1465 1470
Asp Ser Asp Ser Asn Phe Glu Lys Ile Val Ser Lys Ala Val Thr Ser
1475 1480 1485
Lys Lys Ser Lys Gly Glu Ser Asp Asp Phe His Met Asp Phe Asp Ser
1490 1495 1500
Ala Val Ala Pro Arg Ala Lys Ser Val Arg Ala Lys Lys Pro Ile Lys
1505 1510 1515 1520
Tyr Leu Glu Glu Ser Asp Glu Asp Asp Leu Phe
1525 1530

<210> 223
<211> 1111
<212> DNA
<213> Homo sapiens

<400> 223
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acgccatcaa gaagaagatg cagatgctga agctcgacaa ggagaacgcc ttggatcgag 120
ctgagcaggc ggaggccgac aagaaggcgg cggaagacag gagcaagcag ctggaagatg 180
agctggtgtc actgcaaaag aaactcaagg gcaccgaaga tgaactggac aaatactctg 240
aggctctcaa agatgcccag gagaagctgg agctggcaga gaaaaaggcc accgatgctg 300
aagccgacgt agcttctctg aacagacgca tccagctggt tgaggaagag ttggatcgtg 360
cccaggagcg tctggcaaca gctttgcaga agctggagga agctgagaag gcagcagatg 420
agagtgagag aggcatgaaa gtcattgaga gtcgagccca aaaagatgaa gaaaaaatgg 480
aaattcagga gatccaactg aaagaggcca agcacattgc tgaagatgcc gaccgcaaat 540
acgaagaggt ggcccgtaag ctggtcatca ttgagagcga cctggaacgt gcagaggagc 600
gggctgagct ctcagaaggc aaatgtgccg agcttgaaga agaattgaaa actgtgacga 660
acaacttgaa gtcactggag gctcaggctg agaagtactc gcagaaggaa gacagatatg 720
aggaagagat caaggtcctt tccgacaagc tgaaggaggc tgagactcgg gctgagtttg 780
cggagaggtc agtaactaaa ttggagaaaa gcattgatga cttagaagac gagctgtacg 840
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cttccatata agtttctttg cttcacttct cccaagactc cctcgtcgag ctggatgtcc 960
cacctctctg agctctgcat ttgtctattc tccagctgac cctggttctc tctcttagca 1020
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tgtcaaataa acactgtgta agctaaaaaa a 1111

<210> 224
<211> 284
<212> PRT
<213> Homo sapiens

<400> 224
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Asn Ala Leu Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala
20 25 30
Glu Asp Arg Ser Lys Gln Leu Glu Asp Glu Leu Val Ser Leu Gln Lys
35 40 45
Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu
50 55 60
Lys Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp
65 70 75 80
Ala Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu
85 90 95
Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys

100 105 110
Leu Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys
115 120 125
Val Ile Glu Ser Arg Ala Gln Lys Asp Glu Glu Lys Met Glu Ile Gln
130 135 140
Glu Ile Gln Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg
145 150 155 160
Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu
165 170 175
Glu Arg Ala Glu Glu Arg Ala Glu Leu Ser Glu Gly Lys Cys Ala Glu
180 185 190
Leu Glu Glu Glu Leu Lys Thr Val Thr Asn Asn Leu Lys Ser Leu Glu
195 200 205
Ala Gln Ala Glu Lys Tyr Ser Gln Lys Glu Asp Arg Tyr Glu Glu Glu
210 215 220
Ile Lys Val Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu
225 230 235 240
Phe Ala Glu Arg Ser Val Thr Lys Leu Glu Lys Ser Ile Asp Asp Leu
245 250 255
Glu Asp Glu Leu Tyr Ala Gln Lys Leu Lys Tyr Lys Ala Ile Ser Glu
260 265 270
Glu Leu Asp His Ala Leu Asn Asp Met Thr Ser Ile
275 280

<210> 225
<211> 501
<212> DNA
<213> Homo sapiens

<400> 225
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aagatggtga agcagatcga gagcaagact gcttttcagg aagccttgga cgctgcaggt 120
gataaacttg tagtagttga cttctcagcc acgtggtgtg ggccttgcaa aatgatcaac 180
cctttctttc attccctctc tgaaaagtat tccaacgtga tattccttga agtagatgtg 240
gatgactgtc aggatgttgc ttcagagtgt gaagtcaaat gcacgccaac attccagttt 300
tttaagaagg gacaaaaggt gggtgaattt tctggagcca ataaggaaaa gcttgaagcc 360
accattaatg aattagtcta atcatgtttt ctgaaaacat aaccagccat tggctattta 420
aacttgtatt tttttattta caaaatataa atatgaagac ataaccagtt gccatctgcg 480
tgacaataaa cattatgcta a 501

<210> 226
<211> 105
<212> PRT
<213> Homo sapiens

<400> 226
Met Val Lys Gln Ile Glu Ser Lys Thr Ala Phe Gln Glu Ala Leu Asp
1 5 10 15
Ala Ala Gly Asp Lys Leu Val Val Val Asp Phe Ser Ala Thr Trp Cys
20 25 30
Gly Pro Cys Lys Met Ile Asn Pro Phe Phe His Ser Leu Ser Glu Lys
35 40 45
Tyr Ser Asn Val Ile Phe Leu Glu Val Asp Val Asp Asp Cys Gln Asp
50 55 60
Val Ala Ser Glu Cys Glu Val Lys Cys Thr Pro Thr Phe Gln Phe Phe
65 70 75 80
Lys Lys Gly Gln Lys Val Gly Glu Phe Ser Gly Ala Asn Lys Glu Lys
85 90 95

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Leu Glu Ala Thr Ile Asn Glu Leu Val
            100                 105


<210> 227
<211> 783
<212> DNA
<213> Homo sapiens

<400> 227
ggcacgagcg agttcctgtc tctctgccaa cgccgcccgg atggcttccc aaaaccgcga 60
cccagccgcc actagcgtcg ccgccgcccg taaaggagct gagccgagcg gggcgccgc 120
ccggggtccg gtgggcaaaa ggctacagca ggagctgatg accctcatga tgtctggcga 180
taaagggatt tctgccttcc ctgaatcaga caacctttc aaatgggtag ggaccatcca 240
tggagcagct ggaacagtat atgaagacct gaggtataag ctctcgctag agttccccag 300
tggctaccct tacaatgcgc ccacagtgaa gttcctcacg ccctgctatc accccaacgt 360
ggacacccag ggtaacatat gcctggacat cctgaaggaa aagtggtctg ccctgtatga 420
tgtcaggacc attctgctct ccatccagag ccttctagga gaacccaaca ttgatagtcc 480
cttgaacaca catgctgccg agctctggaa aaaccccaca gcttttaaga agtacctgca 540
agaaacctac tcaaagcagg tcaccagcca ggagccctga cccaggctgc ccagcctgtc 600
cttgtgtcgt ctttttaatt tttccttaga tggtctgtcc tttttgtgat ttctgtatag 660
gactctttat cttgagctgt ggtatttttg ttttgttttt gtcttttaaa ttaagcctcg 720
gttgagccct tgtatattaa ataaatgcat ttttgtcctt ttttaaaaaa aaaaaaaaaa 780
aaa                                                               783

<210> 228
<211> 179
<212> PRT
<213> Homo sapiens

<400> 228
Met Ala Ser Gln Asn Arg Asp Pro Ala Ala Thr Ser Val Ala Ala Ala
 1               5                  10                  15
Arg Lys Gly Ala Glu Pro Ser Gly Gly Ala Ala Arg Gly Pro Val Gly
            20                  25                  30
Lys Arg Leu Gln Gln Glu Leu Met Thr Leu Met Met Ser Gly Asp Lys
        35                  40                  45
Gly Ile Ser Ala Phe Pro Glu Ser Asp Asn Leu Phe Lys Trp Val Gly
    50                  55                  60
Thr Ile His Gly Ala Ala Gly Thr Val Tyr Glu Asp Leu Arg Tyr Lys
65                  70                  75                  80
Leu Ser Leu Glu Phe Pro Ser Gly Tyr Pro Tyr Asn Ala Pro Thr Val
                85                  90                  95
Lys Phe Leu Thr Pro Cys Tyr His Pro Asn Val Asp Thr Gln Gly Asn
            100                 105                 110
Ile Cys Leu Asp Ile Leu Lys Glu Lys Trp Ser Ala Leu Tyr Asp Val
        115                 120                 125
Arg Thr Ile Leu Leu Ser Ile Gln Ser Leu Leu Gly Glu Pro Asn Ile
    130                 135                 140
Asp Ser Pro Leu Asn Thr His Ala Ala Glu Leu Trp Lys Asn Pro Thr
145                 150                 155                 160
Ala Phe Lys Lys Tyr Leu Gln Glu Thr Tyr Ser Lys Gln Val Thr Ser
                165                 170                 175
Gln Glu Pro


<210> 229
<211> 777
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<212> DNA
<213> Homo sapiens

<400> 229
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gaggaatggg atttaatgac ctttgatgcc aacccatatg acagcgtgaa aaaaatcaaa 120
gaacatgtcc ggtctaagac caaggttcct gtgcaggacc aggttctttt gctgggctcc 180
aagatcttaa agccacggag aagcctctca tcttatggca ttgacaaaga gaagaccatc 240
caccttaccc tgaaagtggt gaagcccagt gatgaggagc tgcccttgtt tcttgtggag 300
tcaggtgatg aggcaaagag gcacctcctc caggtgcgaa ggtccagctc agtggcacaa 360
gtgaaagcaa tgatcgagac taagacgggt ataatccctg agacccagat tgtgacttgc 420
aatggaaaga gactggaaga tgggaagatg atggcagatt acggcatcag aaagggcaac 480
ttactcttcc tggcatctta ttgtattgga gggtgaccac cctggggatg gggtgttggc 540
aggggtcaaa aagcttattt cttttaatct cttactcaac gaacacatct tctgatgatt 600
tcccaaaatt aatgagaatg agatgagtag agtaagattt gggtgggatg ggtaggatga 660
agtatattgc ccaactctat gtttctttga ttctaacaca attaattaag tgacatgatt 720
tttactaatg tattactgag actagtaaat aaatttttaa ggcaaaatag agcattc 777

<210> 230
<211> 165
<212> PRT
<213> Homo sapiens

<400> 230
Met Ala Pro Asn Ala Ser Cys Leu Cys Val His Val Arg Ser Glu Glu
1 5 10 15
Trp Asp Leu Met Thr Phe Asp Ala Asn Pro Tyr Asp Ser Val Lys Lys
20 25 30
Ile Lys Glu His Val Arg Ser Lys Thr Lys Val Pro Val Gln Asp Gln
35 40 45
Val Leu Leu Leu Gly Ser Lys Ile Leu Lys Pro Arg Arg Ser Leu Ser
50 55 60
Ser Tyr Gly Ile Asp Lys Glu Lys Thr Ile His Leu Thr Leu Lys Val
65 70 75 80
Val Lys Pro Ser Asp Glu Glu Leu Pro Leu Phe Leu Val Glu Ser Gly
85 90 95
Asp Glu Ala Lys Arg His Leu Leu Gln Val Arg Arg Ser Ser Ser Val
100 105 110
Ala Gln Val Lys Ala Met Ile Glu Thr Lys Thr Gly Ile Ile Pro Glu
115 120 125
Thr Gln Ile Val Thr Cys Asn Gly Lys Arg Leu Glu Asp Gly Lys Met
130 135 140
Met Ala Asp Tyr Gly Ile Arg Lys Gly Asn Leu Leu Phe Leu Ala Ser
145 150 155 160
Tyr Cys Ile Gly Gly
165

<210> 231
<211> 4797
<212> DNA
<213> Homo sapiens

<400> 231
gcagtgaaca caacctttcc cctgagccac tggaattgga cagaatgccc cattctcctc 60
tgatctccat tcctcatgtg tggtgtcacc cagaagagga ggaaagaatg catgatgaac 120
ttctacaagc agtatccaag ggccggtga tgttcaggga tgtttccata gacttctctc 180
aagaggaatg ggaatgcctg gacgctgatc agatgaattt atacaaagaa gtgatgttgg 240
agaatttcag caacctggtt tcagtgggac tttccaattc taagccagct gtgatctcct 300

tattggaaca aggaaaagag ccctggatgg ttgatagaga gctgactaga ggcctgtgtt 360
cagatctgga atcaatgtgt gagaccaaaa tattatctct aaagaagaga catttcagtc 420
aagtaataat tacccgtgaa gacatgtcta cttttattca gcccacattt cttattccac 480
ctcaaaaaac tatgagtgaa gagaaaccat gggaatgtaa gatatgtgga aagaccttta 540
atcaaaactc acaatttatc caacatcaga gaattcattt tggtgaaaaa cactatgaat 600
ctaaggagta tgggaagtcc tttagtcgtg gctcactcgt tactcgacat cagaggattc 660
acactggtaa aaaaccctat gaatgtaagg aatgtggcaa ggcttttagt tgtagttcat 720
atttttctca acatcagagg attcacactg gtgagaaacc ctatgaatgt aaggaatgtg 780
gaaaagcctt taagtattgc tcaaacctta atgatcatca gagaattcac actggtgaga 840
aaccctatga atgtaaagta tgtggaaaag cctttactaa aagttcacaa ctttttctac 900
atctgagaat tcatactggt gagaaacctt atgaatgtaa agaatgtggg aaagccttta 960
ctcaacactc aaggcttatt cagcatcaga gaatgcatac tggtgagaaa ccttatgaat 1020
gtaagcagtg tgggaaggcc tttaatagtg cctcaacact tactaaccat cacagaattc 1080
atgctggtga gaagctctat gaatgtgaag aatgtagaaa ggcctttatt cagagctcag 1140
aacttattca acatcagaga atccatacag atgaaaaacc atatgaatgt aatgaatgtg 1200
ggaaggcctt taataaaggc tcaaatctta ctcgacatca gagaattcac actggtgaga 1260
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tatgtattcg tttttaaacg atacgataac aaagtaccaa gtaccaaaac cttggtggct 1500
taaaacaaga gaaatttatt ctctcatagt ttagagcctg gaaatctaaa ctcaagggtg 1560
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aacctccagc tcctgagttc aagcgattct tgtgcctcag cctctcaagt agttgggatt 2100
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tatcagcaga aactatatgc acatattaga aaacctagag gaagtggata aattcctaga 3300
aacacataac cttccaagat tgaaccaggg agaaatagga atcctcaaca gactactgag 3360
tattgaaatt gaatcagtaa tagaaaaaaa tcttgcaaaa acaaaaagcc caggaccaga 3420
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acacctgtaa tcccagcact ttgcaaggcc aaggcgggca gatcacatga tgtcaagagt 3840

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ttgagaccag tctggctgac atggcgaaac cctgtctcta ctaaaaatag aaaaattggc 3900
tgggcatggt ggcaggcact gtagtcccag ctacttggga ggctgaggca ggagaattac 3960
ttgaacctga gaagcggagg ttgcagtgag ctgagatagt gccattgcac tccagcctgg 4020
gcaacagagc aaattgcttg aatgtgggag gtggaggttg cagtgagccg agattatgcc 4080
attgcactcc agccgggga gcaacaaagc cagactccat ctcaaaaaaa aaccaaaaaa 4140
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gttactataa actcttctgt ttctccatca cgttgttggt catctttact gattacaaat 4740
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<210> 232
<211> 433
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 433
<223> Xaa = Any Amino Acid

<400> 232

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Met Pro His Ser Pro Leu Ile Ser Ile Pro His Val Trp Cys His Pro
 1               5                  10                  15
Glu Glu Glu Glu Arg Met His Asp Glu Leu Leu Gln Ala Val Ser Lys
            20                  25                  30
Gly Pro Val Met Phe Arg Asp Val Ser Ile Asp Phe Ser Gln Glu Glu
        35                  40                  45
Trp Glu Cys Leu Asp Ala Asp Gln Met Asn Leu Tyr Lys Glu Val Met
    50                  55                  60
Leu Glu Asn Phe Ser Asn Leu Val Ser Val Gly Leu Ser Asn Ser Lys
65                  70                  75                  80
Pro Ala Val Ile Ser Leu Leu Glu Gln Gly Lys Glu Pro Trp Met Val
                85                  90                  95
Asp Arg Glu Leu Thr Arg Gly Leu Cys Ser Asp Leu Glu Ser Met Cys
            100                 105                 110
Glu Thr Lys Ile Leu Ser Leu Lys Lys Arg His Phe Ser Gln Val Ile
        115                 120                 125
Ile Thr Arg Glu Asp Met Ser Thr Phe Ile Gln Pro Thr Phe Leu Ile
    130                 135                 140
Pro Pro Gln Lys Thr Met Ser Glu Glu Lys Pro Trp Glu Cys Lys Ile
145                 150                 155                 160
Cys Gly Lys Thr Phe Asn Gln Asn Ser Gln Phe Ile Gln His Gln Arg
                165                 170                 175
Ile His Phe Gly Glu Lys His Tyr Glu Ser Lys Glu Tyr Gly Lys Ser
            180                 185                 190
Phe Ser Arg Gly Ser Leu Val Thr Arg His Gln Arg Ile His Thr Gly
        195                 200                 205
Lys Lys Pro Tyr Glu Cys Lys Glu Cys Gly Lys Ala Phe Ser Cys Ser
    210                 215                 220
Ser Tyr Phe Ser Gln His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr
225                 230                 235                 240
Glu Cys Lys Glu Cys Gly Lys Ala Phe Lys Tyr Cys Ser Asn Leu Asn
```

```
                245                 250                 255
Asp His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Glu Cys Lys Val
            260                 265                 270
Cys Gly Lys Ala Phe Thr Lys Ser Ser Gln Leu Phe Leu His Leu Arg
        275                 280                 285
Ile His Thr Gly Glu Lys Pro Tyr Glu Cys Lys Glu Cys Gly Lys Ala
    290                 295                 300
Phe Thr Gln His Ser Arg Leu Ile Gln His Gln Arg Met His Thr Gly
305                 310                 315                 320
Glu Lys Pro Tyr Glu Cys Lys Gln Cys Gly Lys Ala Phe Asn Ser Ala
                325                 330                 335
Ser Thr Leu Thr Asn His His Arg Ile His Ala Gly Glu Lys Leu Tyr
            340                 345                 350
Glu Cys Glu Glu Cys Arg Lys Ala Phe Ile Gln Ser Ser Glu Leu Ile
        355                 360                 365
Gln His Gln Arg Ile His Thr Asp Glu Lys Pro Tyr Glu Cys Asn Glu
    370                 375                 380
Cys Gly Lys Ala Phe Asn Lys Gly Ser Asn Leu Thr Arg His Gln Arg
385                 390                 395                 400
Ile His Thr Gly Glu Lys Pro Tyr Asp Cys Lys Glu Cys Gly Lys Ala
                405                 410                 415
Phe Gly Ser Arg Ser Asp Leu Ile Arg His Glu Gly Ile His Thr Gly
            420                 425                 430
Xaa
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<210> 233
<211> 1860
<212> DNA
<213> Homo sapiens

<400> 233

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ggccccggcc tcgccgcccc gcgcagtacc cagcccggcc ccgccgaccc gcctctactg 120
ccggctccgc gcccttcccc gagggctgga tgatgggctg tttcgccctg caaacggtgg 180
acaccgagct gaccgcggac tcggtggagt ggtgcccgct gcaaggctgc aggcacctgc 240
tggcgtgcgg gacctaccag ctgcggcggc cggaggaccg gcctgccggc ccccagaaca 300
agggtggaat ggaagttaag gagcctcagg tccgtttagg ccgtctcttc ctgtacagtt 360
tcaatgacaa caactctatt caccctctgg tcgaggtcca aagaaaagat acttctgcaa 420
tcctggacat gaaatggtgt cacatcccgg tggctggaca tgccctcttg ggcttggcag 480
atgccagtgg atccatacaa ctgctccgcc tggtggaatc tgagaagagc cacgtgctgg 540
agccattgtc cagccttgcc ctggaggagc agtgtctggc tttgtcccta gattggtcca 600
ctgggaaaac tggaagggcc ggggaccagc ccttgaagat catcagcagt gactccacag 660
ggcagctcca cctcctgatg gtgaatgaga cgaggcccag gctgcagaaa gtggcctcat 720
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tgtattcagg gggcgacgat ggccttctga ggggctggga caccagggta cccggcaaat 840
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gaccccagag tggaatgaag ccactcacag agggcatgag gaagaatggc acctggctgc 1380
aggctacagc agccaccaca cgtgactgtg gcgtgaaccc agaagaagca gactcagcct 1440
tcagcctcct ggccacctgc tccttctatg accatgcgct ccacctctgg gagtgggagg 1500
ggaactgagc ttgaaatcat gaagcccctt cccacaagga aaccaggagg gagactgcga 1560
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gtgagtgccc gggaccacct catcagagat gcttactgca gccctgcagg tgcctgggca 1620
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ctgggcccct gaaagtggac tgggtgattc tgtctggcag agagtgggga aaagacgcgg 1740
tttccagctt gcagatttgt taagtttctc aggcagattt tgactttcag cctttcatac 1800
ttgtttaagc aactatttgt attaaatgaa gtttttgaa aaaaaaaaaa aaaaaaaaaa 1860

<210> 234
<211> 501
<212> PRT
<213> Homo sapiens

<400> 234
Asp Pro Arg Val Arg Ala Arg Ala Asp Gly Val Pro Gly Ala Leu Arg
1 5 10 15
Ser Ser Gly Arg Pro Arg Pro Arg Arg Pro Ala Gln Tyr Pro Ala Arg
20 25 30
Pro Arg Arg Pro Ala Ser Thr Ala Gly Ser Ala Pro Phe Pro Glu Gly
35 40 45
Trp Met Met Gly Cys Phe Ala Leu Gln Thr Val Asp Thr Glu Leu Thr
50 55 60
Ala Asp Ser Val Glu Trp Cys Pro Leu Gln Gly Cys Arg His Leu Leu
65 70 75 80
Ala Cys Gly Thr Tyr Gln Leu Arg Arg Pro Glu Asp Arg Pro Ala Gly
85 90 95
Pro Gln Asn Lys Gly Gly Met Glu Val Lys Glu Pro Gln Val Arg Leu
100 105 110
Gly Arg Leu Phe Leu Tyr Ser Phe Asn Asp Asn Asn Ser Ile His Pro
115 120 125
Leu Val Glu Val Gln Arg Lys Asp Thr Ser Ala Ile Leu Asp Met Lys
130 135 140
Trp Cys His Ile Pro Val Ala Gly His Ala Leu Leu Gly Leu Ala Asp
145 150 155 160
Ala Ser Gly Ser Ile Gln Leu Leu Arg Leu Val Glu Ser Glu Lys Ser
165 170 175
His Val Leu Glu Pro Leu Ser Ser Leu Ala Leu Glu Glu Gln Cys Leu
180 185 190
Ala Leu Ser Leu Asp Trp Ser Thr Gly Lys Thr Gly Arg Ala Gly Asp
195 200 205
Gln Pro Leu Lys Ile Ile Ser Ser Asp Ser Thr Gly Gln Leu His Leu
210 215 220
Leu Met Val Asn Glu Thr Arg Pro Arg Leu Gln Lys Val Ala Ser Trp
225 230 235 240
Gln Ala His Gln Phe Glu Ala Trp Ile Ala Ala Phe Asn Tyr Trp His
245 250 255
Pro Glu Ile Val Tyr Ser Gly Gly Asp Asp Gly Leu Leu Arg Gly Trp
260 265 270
Asp Thr Arg Val Pro Gly Lys Phe Leu Phe Thr Ser Lys Arg His Thr
275 280 285
Met Gly Val Cys Ser Ile Gln Ser Ser Pro His Arg Glu His Ile Leu
290 295 300
Ala Thr Gly Ser Tyr Asp Glu His Ile Leu Leu Trp Asp Thr Arg Asn
305 310 315 320
Met Lys Gln Pro Leu Ala Asp Thr Pro Val Gln Gly Gly Val Trp Arg
325 330 335
Ile Lys Trp His Pro Phe His His His Leu Leu Leu Ala Ala Cys Met
340 345 350
His Ser Gly Phe Lys Ile Leu Asn Cys Gln Lys Ala Met Glu Glu Arg
355 360 365

```
Gln Glu Ala Thr Val Leu Thr Ser His Thr Leu Pro Asp Ser Leu Val
    370                 375                 380
Tyr Gly Ala Asp Trp Ser Trp Leu Leu Phe Arg Ser Leu Gln Arg Ala
385                 390                 395                 400
Pro Ser Trp Ser Phe Pro Ser Asn Leu Gly Thr Lys Thr Ala Asp Leu
                405                 410                 415
Lys Gly Ala Ser Glu Leu Pro Thr Pro Cys His Glu Cys Arg Glu Asp
            420                 425                 430
Asn Asp Gly Glu Gly His Ala Arg Pro Gln Ser Gly Met Lys Pro Leu
        435                 440                 445
Thr Glu Gly Met Arg Lys Asn Gly Thr Trp Leu Gln Ala Thr Ala Ala
    450                 455                 460
Thr Thr Arg Asp Cys Gly Val Asn Pro Glu Glu Ala Asp Ser Ala Phe
465                 470                 475                 480
Ser Leu Leu Ala Thr Cys Ser Phe Tyr Asp His Ala Leu His Leu Trp
                485                 490                 495
Glu Trp Glu Gly Asn
            500
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<210> 235
<211> 1614
<212> DNA
<213> Homo sapiens

<400> 235
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caaccagctg actcccgtag aggaagacac tgtggaggcc agttctggag ctattgcagc 120
ctcggttgcc cggccgggga cccgagccga aaagttatcg tcagaatgtc gggcaaagac 180
cgaattgaaa tctttccctc gcgaatggca cagaccatca tgaaggctcg tttaaaggga 240
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cagatcctaa agaagataat agagactaaa atgttgatgg gcgaagtgat gagagaagct 360
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<211> 247
<212> PRT
<213> Homo sapiens
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35 40 45
Lys Lys Ile Ile Glu Thr Lys Met Leu Met Gly Glu Val Met Arg Glu
50 55 60
Ala Ala Phe Ser Leu Ala Glu Ala Lys Phe Thr Ala Gly Asp Phe Ser
65 70 75 80
Thr Thr Val Ile Gln Asn Val Asn Lys Ala Gln Val Lys Ile Arg Ala
85 90 95
Lys Lys Asp Asn Val Ala Gly Val Thr Leu Pro Val Phe Glu His Tyr
100 105 110
His Glu Gly Thr Asp Ser Tyr Glu Leu Thr Gly Leu Ala Arg Gly Gly
115 120 125
Glu Gln Leu Ala Lys Leu Lys Arg Asn Tyr Ala Lys Ala Val Glu Leu
130 135 140
Leu Val Glu Leu Ala Ser Leu Gln Thr Ser Phe Val Thr Leu Asp Glu
145 150 155 160
Ala Ile Lys Ile Thr Asn Arg Arg Val Asn Ala Ile Glu His Val Ile
165 170 175
Ile Pro Arg Ile Glu Arg Thr Leu Ala Tyr Ile Ile Thr Glu Leu Asp
180 185 190
Glu Arg Glu Arg Glu Glu Phe Tyr Arg Leu Lys Lys Ile Gln Glu Lys
195 200 205
Lys Lys Ile Leu Lys Glu Lys Ser Glu Lys Asp Leu Glu Gln Arg Arg
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<210> 237
<211> 1658
<212> DNA
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gaagcctttg agcagctcca ggccaagaaa caaatggcca tggagaaacg cagagcagtc 480
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<210> 238
<211> 277
<212> PRT
<213> Homo sapiens

<400> 238

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Glu Leu Pro Ala Lys Ile Leu Val Glu Phe Val Val Asp Ser Gln Lys
        35                  40                  45
Lys Asp Lys Leu Leu Cys Ser Gln Leu Gln Val Ala Asp Phe Leu Gln
    50                  55                  60
Asn Ile Leu Ala Gln Glu Asp Thr Ala Lys Gly Leu Asp Pro Leu Ala
65                  70                  75                  80
Ser Glu Asp Thr Ser Arg Gln Lys Ala Ile Ala Ala Lys Glu Gln Trp
                85                  90                  95
Lys Glu Leu Lys Ala Thr Tyr Arg Glu His Val Glu Ala Ile Lys Ile
            100                 105                 110
Gly Leu Thr Lys Ala Leu Thr Gln Met Glu Glu Ala Gln Arg Lys Arg
        115                 120                 125
Thr Gln Leu Arg Glu Ala Phe Glu Gln Leu Gln Ala Lys Lys Gln Met
    130                 135                 140
Ala Met Glu Lys Arg Arg Ala Val Gln Asn Gln Trp Gln Leu Gln Gln
145                 150                 155                 160
Glu Lys His Leu Gln His Leu Ala Glu Val Ser Ala Glu Val Arg Glu
                165                 170                 175
Arg Lys Thr Gly Thr Gln Gln Glu Leu Asp Gly Val Phe Gln Lys Leu
            180                 185                 190
Gly Asn Leu Lys Gln Gln Ala Glu Gln Glu Arg Asp Lys Leu Gln Arg
        195                 200                 205
Tyr Gln Thr Phe Leu Gln Leu Leu Tyr Thr Leu Gln Gly Lys Leu Leu
    210                 215                 220
Phe Pro Glu Ala Glu Ala Glu Ala Glu Asn Leu Pro Asp Asp Lys Pro
225                 230                 235                 240
Gln Gln Pro Thr Arg Pro Gln Glu Gln Ser Thr Gly Asp Thr Met Gly
                245                 250                 255
Arg Asp Pro Gly Val Ser Phe Lys Ala Val Gly Leu Gln Pro Ala Gly
            260                 265                 270
Asp Val Asn Leu Pro
        275
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